American Journal of Diseases of Children

VOLUME 61 JUNE 1941 NUMBER 6

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INFECTIOUS MONONUCLEOSIS

WITH SPECIAL REFERENCE TO CEREBRAL COMPLICATIONS

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The American pediatric literature has singularly few discussions on infectious mononucleosis, or glandular fever, though numerous authors in other fields have referred to the condition as primarily an infection of childhood. There is a plausible explanation for this lack of interest among pediatricians. In general, authors have accepted reports of epidemics of glandular fever as referring to a disease identical with sporadic infectious mononucleosis, and they not infrequently have spoken of two types, endemic and epidemic, of glandular fever. However, as Tidy,[1] who gave an excellent historical account of the disease, has pointed out, for thirty years after 1889, when Pfeiffer[2] first described *Drüsenfieber,* or glandular fever, case reports were based on clinical data only. Although many of these reports obviously reflect careful clinical observations, less critical enthusiasts in all probability included cases that could not stand the diagnostic criteria of the more recent discoveries about the pathologic blood picture and the heterophile agglutination test. Since cases in which there were suppurating cervical adenitis and acute hemorrhagic nephritis have been included in the series reported, the skepticism of American pediatricians is at least understandable. Davis[3] in 1929 reported on a small epidemic of glandular fever among infants in which blood studies revealed lymphocytosis. In 1935 Nolan[4] reported briefly on an epidemic among the children of the navy personnel at Coronado, Calif., in which both blood studies and heterophile agglutination tests were carried out, but he gave so few

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1. Tidy, H. L.: Glandular Fever and Infectious Mononucleosis, Lancet **2**:180 and 236, 1934.

2. Pfeiffer, E.: Drüsenfieber, Jahrb. f. Kinderh. **29**:257, 1889.

3. Davis, C. M.: Acute Glandular Fever of Pfeiffer: Report of Nursery Epidemic, J. A. M. A. **92**:1417 (April 27) 1929.

4. Nolan, R. A.: Report of So-Called Epidemic of Glandular Fever (Infectious Mononucleosis), U. S. Nav. M. Bull. **33**:479, 1935.

details that it is hard to evaluate his observations. It has seemed to us, therefore, that until epidemics of glandular fever in infancy and childhood and sporadic cases of infectious mononucleosis have been convincingly proved to have a common cause it is better to limit the discussion of the disease in childhood to the classic cases. This does not mean that epidemics did not or may not occur; it means only that discussion should be withheld until further studies have clarified the situation.

Although the cause of infectious mononucleosis is still unknown, studies on the pathologic changes in the blood were begun between 1918 and 1920, and the report on heterophile antibodies by Paul and Bunnell [5] in 1932 greatly increased interest in the disease and made it possible to clarify and to evaluate the clinical diagnosis of the condition. In recent years most of the studies on large numbers of patients [6] have been made in student health clinics, but many authors have referred to occurrences of the disease in young children.

CLINICAL DATA FOR SIX PATIENTS WITH INFECTIOUS MONONUCLEOSIS

In table 1 are presented data for 6 patients encountered in private practice who showed the classic clinical, hematologic and serologic signs of infectious mononucleosis. Four patients were 12 years old or younger, and 2 were in late adolescence; among them there was no appreciable variation in signs related to age.

There has been a considerable tendency for authors to classify the disease into such types as glandular, anginose, febrile, abdominal and cerebral, thereby creating the impression that the disease not only is extremely difficult to diagnose but may be readily confused with other conditions or be the correct diagnosis for a host of misdiagnosed obscure illnesses. This is contrary to our experience. Even though the presenting complaint, as may be noted in table 1, may vary considerably, in our cases the first physical examination almost invariably suggested the diagnosis so strongly that mononucleosis was mentioned to the patient's family and included in our daily notes on the case as a likely possibility. Furthermore, during the last two years numerous children with obscure illnesses have been studied both hematologically and serologically without the presence of mononucleosis being disclosed. Only a few confusing cases have been encountered, and these will be discussed later.

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5. Paul, J. R., and Bunnell, W. W.: The Presence of Heterophile Antibodies in Infectious Mononucleosis, Am. J. M. Sc. **183**:90, 1932.

6. McKinlay, C. A.: Infectious Mononucleosis: Clinical Aspects, J. A. M. A. **105**:761 (Sept. 7) 1935. Lyght, C. E.: Infectious Mononucleosis, Journal-Lancet **58**:91, 1938. Templeton, H. J., and Sutherland, R. T.: The Exanthem of Acute Mononucleosis, J. A. M. A. **113**:1215 (Sept. 23) 1939.

J. C. (patient 1, table 1) had an acute onset of the disease, with relatively high fever and sore throat (anginose). The membrane on the tonsils and the foul breath suggested diphtheria; however, further examination revealed enlargement not only of the anterior cervical nodes but of the posterior cervical, suboccipital, axillary and inguinal nodes and marked enlargement of the spleen. The child had been immunized to diphtheria and had had a negative reaction to a Schick test. The good color and general well-being made leukemia a less likely diagnosis than mononucleosis. The studies on the blood and the results of the heterophile agglutination test confirmed the clinical impression. Recovery was rapid. The temperature returned to normal on the third day, the condition of the throat reverted to normal in a week and the spleen remained palpable for only two weeks. The results of various leukocyte counts are recorded in table 1.

H. H. (patient 2) had an acute onset of the disease with high fever and a few foul-smelling stools (signs of the "abdominal" type of mononucleosis). Although there were no complaints referable to the throat, examination showed hypertrophy of the lymphoid tissue and later ulceration and exudate. The spleen was slightly enlarged. Although typhoid had to be considered as a diagnosis, from the onset the child did not appear as ill or as toxic as a patient with typhoid, and in this instance, too, mononucleosis was suggested as a probability at the time of the first visit.

M. T., B. P. and E. S. (patients 3, 4 and 5) had typical signs of the so-called febrile type of mononucleosis—malaise, slight fever, anorexia and some tenderness of the glands. In each instance the glandular and splenic enlargement suggested the diagnosis.

M. M. (patient 6) had a distinctly "cerebral" type of the disease; but even though headache was severe, she did not appear very ill, and the rest of the symptoms were so characteristic of mononucleosis that she was not hospitalized for lumbar puncture. Other cases in which there were more pronounced signs referable to the central nervous system are discussed later.

The cases of patients 1 to 4 in no way differ from the cases of mononucleosis in young adults which have been reported. Data for the 2 patients in late adolescence were purposely included to illustrate the uniformity of the clinical picture regardless of age. It is probably true, however, that preadolescent patients have a shorter course and less frequent relapses than do adults.

OBSERVATIONS FROM CASES OF INFECTIOUS MONONUCLEOSIS

Etiology.—The etiologic agent of infectious mononucleosis is unknown but is generally believed to be a virus. Bacteriologic studies of material from the throat have yielded no consistent results. Vincent's organism, spirochetes and fusiform bacilli have been found many

TABLE 1.—*Data for Six Patients with Infectious Mononucleosis*

Patient	Sex	Age, Years	Clinical Data	Results of White Cell Counts						
				Date	Total Leukocytes per Cu. Mm.	Polymorphonuclears, per Cent	Lymphocytes, per Cent	Monocytes, per Cent	Eosinophils, per Cent	Heterophile Agglutination Titer
J. C.	M	4	Temperature 102.6 F.; sore throat; foul breath; tonsils swollen, with exudate that resembled a diphtheritic membrane; anterior and posterior cervical, suboccipital and postauricular glands enlarged; spleen near the umbilicus; patient did not appear ill	10/ 8/40	19,200	12	85	3	..	.....
				10/11/40	15,100	9	89	..	2	1:640
				10/16/40	10,200	16	78	5	1	.....
				10/30/40	8,400	15	79	3	3	.....
H. H.	M	9½	Temperature 104.6 F., dropped by lysis over period of 1 week; malaise and sore throat from 4th to 6th day; patient not toxic; lymphoid tissue of throat was swollen and later had exudate on it; spleen just palpable; cervical glands slightly enlarged	8/24/40	6,100	63	16	4	..	.....
				8/28/40	13,200	37	49	14	..	1:160
M. T.	M	11½	Abdominal pain; pain on swallowing; fever and malaise of indefinite duration and insidious onset; tonsils large, with exudate in crypts; spleen markedly and inguinal glands slightly enlarged; temperature 100.2 F. on first examination; after 1 week all glands were enlarged	3/11/40	11,600	20	75	3	2	1:20
				3/20/40	12,600	27	68	5	..	1:640
						44	44	3	8	1:320
B. P.	M	12	Malaise; later sore throat; temperature 99 to 100 F.; slight enlargement of glands early and slight redness of throat; at end of 1 week spleen and all glands enlarged	9/19/38	9,300	20	79	1	..	.....
				9/20/38	9,100	22	73	2	..	1:80
				9/22/38	8,000	23	75	1	1	.....
				9/30/38	7,900	16	70	7	2	.....
				10/14/38	7,000	30	60	6	4	1:80
				11/ 5/38	9,000	40	37	17	6	.....
E. S.	M	17	Malaise; sore throat; temperature 99 to 100.6 F. for 10 days; conjunctivas injected; tonsils had been removed; lymphoid tissue showed hypertrophy and scattered exudate; cervical, axillary and inguinal glands enlarged; spleen large, thick and firm	10/ 9/39	9,800	27	70	1	2	1:5,280
				10/17/39	.....	11	81	4	2	1:640
				10/27/39	6,700	33	63	3	1	.....
				12/ 4/39	5,500	38	56	5	1	.....
				1/ 9/40	9,200	49	45	3	3	.....
				2/20/40	8,700	36	53	5	6	.....
M. M.	F	19	Temperature 101 F.; intense headache; vomiting; patient not very ill; slight stiffness of neck; throat injected; anterior cervical glands much enlarged, suboccipital large and tender and inguinal and axillary slightly enlarged; spleen palpable	7/ 4/39	9,600	32	65	3	..	.....
				7/ 7/39	.....	13	74	12	1	1:16,384
				7/14/39	6,600	37	67	6	..	.....
				8/ 8/39	10,600	65	30	5	..	1:5,120

times and it has been suggested by some authors that they have etiologic significance, but the general belief is that their presence is coincidental. Most authors have reported that cultures of the blood and spinal fluid gave consistently negative results. An exception is the report of Schmidt and Nyfeldt,[7] who found listerellas in 4 of 5 cases studied; in 2 cases the organism was recovered from the blood as well as from the spinal fluid and in 2 from the spinal fluid alone. These results, to our knowledge, have not been duplicated. Bacteriologic study of biopsy material from glands has yielded negative results.

The most promising research has been carried out by the inoculation of animals. Bland[8] reported that a disease resembling human mononucleosis was produced in a rabbit by inoculation, and he was able to retain the virus through several animal passages. Wising[9] reported that a disease was successfully produced in monkeys by inoculation with an emulsion of a gland removed for biopsy and also that an accidental infection of a laboratory worker had occurred. While removing a gland from an infected monkey the worker cut his finger, and seven days later a glandular syndrome similar to mononucleosis developed, with lymphocytosis and a positive reaction to the heterophile agglutination test.

These studies, as well as the clinical manifestations, strongly imply that a virus is the etiologic agent.

Epidemiology.—As was noted earlier, several authors have spoken of endemics and epidemics of the disease. At present in the United States cases have been reported as occurring endemically or sporadically. Although in all probability the disease is contagious, its communicability must be low. Occasionally 2 members of a family or several persons living in a fraternity house have contracted the disease. In our series, unless the sisters with meningitis and lymphocytosis are accepted as having mononucleosis, no second member of a family contracted the disease, although in all but 1 instance there were other older or younger children in the family.

Whether an attack of the disease produces immunity is unknown, but it probably does not; recurrences have been described and relapses are not uncommon.

Age.—The age incidence at present cannot be accurately stated. Many of the early epidemics of glandular fever were reported as occurring among children or infants. The nature of the disease was not verified by studies on the blood and heterophile agglutination tests; so instances of infections other than mononucleosis may have been

7. Schmidt, V., and Nyfeldt, A.: Ueber Mononucleosis infectiosa und Meningoencephalitis, Acta oto-laryng. **26**:680, 1938.

8. Bland, J. O. W.: Glandular Fever, Lancet **2**:521, 1930.

9. Wising, P. J.: Some Experiments with Lymph Gland Material from Cases of Infectious Mononucleosis, Acta med. Scandinav. **98**:328, 1939.

included, with a consequent increase in the reported incidence of the disease among children. Most of the recent reports have been from student health services in colleges and universities and from hospital groups. These may also give a false impression of the age distribution because of the interest in the disease in such medical organizations and the ease with which students are studied. The disease is not necessarily incapacitating; employed persons may continue to work even though they do not feel well, and they are less likely to consult a physician for an indisposition than are students. Physicians in practice also are less likely to make hematologic and serologic tests for patients with minor illnesses than are physicians in colleges. Also, younger patients are usually seen in the home, and laboratory studies are not made except when the illness is severe or the physician is particularly interested in a syndrome. Our youngest patient who was proved to have the disease was 4 years of age; if the 2 girls with lymphocytosis and meningitis (table 3) are accepted as having the disease, our youngest patient was 2½ years old. We know of an adult more than 50 years old who had the disease. Determination of the true age distribution awaits further observation. At present, the disease appears to be most prevalent among young adults and less frequent among older as well as younger persons.

Sex.—In the cases reported there are more male than female patients, but both sexes are susceptible to the disease.

Signs and Symptoms.—Characteristically, the patient with infectious mononucleosis has fever, anorexia, malaise and often large or tender glands, sore throat and headache. These symptoms may be insidious in onset, the patient being sick or indisposed for several days or more before a physician is consulted, or onset may be acute and sufficiently severe to necessitate immediate confinement to bed. The elevation of temperature may be slight (99 F.) or marked (103 F. or more) and is of variable duration, lasting from two or three days to two or three weeks. The temperature may remain at a high level for several days and drop by lysis, as in typhoid fever, or there may be morning remissions throughout the course.

Changes in the Throat: Often, especially when sore throat is a complaint, examination shows marked, acute pathologic changes, with exudate that may resemble a diphtheritic membrane or the condition characteristic of Vincent's angina. The breath may be foul. Even when no soreness is noted, there is usually hypertrophy of the lymphoid tissue of the pharynx and the tonsillar fossae, often with exudate. The changes in the throat may be late in making their appearance and at times are not noted until the second or third week of the illness.

The Glandular Enlargement: This symptom is variable; the posterior cervical nodes most frequently show the first and the greatest

enlargement, but the anterior cervical glands are almost invariably involved, and not infrequently the suboccipital, the postauricular and even the parotid lymph nodes swell noticeably and may be as tender as in German measles. The axillary and inguinal and at times the epitrochlear glands are distinctly enlarged. The glands remain discrete, with little or no pain or tenderness, and do not suppurate. In some instances the primary and most marked enlargement has been elsewhere than in the glands of the throat, notably in the inguinal glands.

Splenic Enlargement: The spleen usually enlarges enough to be palpable at some time during the illness, and it frequently remains large and firm and extends almost to the umbilicus for days or weeks.

Conjunctivitis: This symptom is not uncommon.

Rash: This symptom has been described in 10 to 18 per cent of the cases. It, too, is variable in extent, duration and type. It is usually macular or maculopapular and morbilliform and resembles the exanthem of German measles. It may be present only over the abdomen and resemble the "rose spots" of typhoid fever. In many cases transient or evanescent rashes are described.

Jaundice: In almost every large series of cases occasional occurrence of this symptom is reported.

Abdominal Pain: In some cases the pain has simulated appendicitis and led to surgical intervention. Enlargement of the mesenteric glands has been found in some cases in which operation was performed.

Headache: This is a common complaint, but it usually is not accompanied by stiffness of the neck or other signs referable to the central nervous system. That actual involvement of the central nervous system does occur is illustrated by the cases reported in this paper.

Renal Involvement: Nephritis or bleeding from the kidney has been described in apparently authentic cases of the disease. The fairly high incidence of this complication in some epidemics of "glandular fever" may have been due to the inclusion of cases of common cervical adenitis due to a streptococcic infection of the throat. Caution must be used in ascribing symptoms and complications to mononucleosis on the basis of early reports of cases of glandular fever, in which diagnosis was made by means of clinical symptoms alone.

Blood Picture.—Although reports on occasional blood studies appeared earlier,[10] the blood changes characteristic of infectious mononucleosis first aroused real interest between 1918 and 1920, when attention was directed to it because the blood picture in this disease had been confused with that of lymphatic leukemia. The classic studies of Downey and McKinlay [11] clarified the subject, although even now in

10. Türk, W. M.: Septische Erkrankungen bei Verkümmerung des Granulozytensystems, Wien. klin. Wchnschr. **20**:157, 1907. Tidy.[1]

11. Downey, H., and McKinlay, C. A.: Acute Lymphadenosis Compared with Acute Lymphatic Leukemia, Arch. Int. Med. **32**:82 (July) 1923.

an occasional case the disease is diagnosed as leukemia. The hemoglobin content and red cell counts remain normal or show only the slight changes characteristic of any illness. The leukocytes may vary in number from slightly below normal to definitely above normal (20,000 to 25,000 per cubic millimeter, and elevations to 40,000 or even to 60,000 have been described. In most reported cases the range is from 6,000 to 20,000. There is a more or less marked increase in the proportion of lymphocytes, which may reach 85 or 90 per cent or more, even though the patient is an adult. The lymphocytes are normal small or large forms, with a varying number of mononuclear cells, which most hematologists place in the lymphocyte series. Early in the disease the blood picture may not be characteristic, and single blood counts, therefore, may fail to give a clue to the diagnosis. In some instances the blood picture returns to normal quickly; in others the abnormality is discernible for months.

Heterophile Agglutinations.—In 1932 Paul and Bunnell,[5] while working with heterophile agglutination tests, encountered high titers of antibodies in the blood of some patients, and these authors later observed that this phenomenon occurred exclusively in the blood of persons with infectious mononucleosis. This observation has been confirmed by other workers.[12] Certain modifications in the test have been made. The titer is usually so high that there is no doubt about the positiveness of the test; titers of 1:5,000 and 1:16,000 were encountered in our small series of cases. The lowest acceptable titer has been placed by various workers at 1:10, 1:20 and 1:64. Apparently, judging from reports in the literature, a titer of 1:64 is acceptable to European authors as indicating the presence of mononucleosis. Since the antibodies are sometimes only transiently present, there probably will always be cases in which the titer is low or is not discovered, but until more is known about the etiology of the disease, a low titer should not be accepted as a positive diagnostic sign in the absence of clinical symptoms or a characteristic blood picture. If the presence of the disease is suspected clinically and the agglutination test gives a negative result, the test should be repeated in more than one laboratory.

Many authors have reported a slightly to a moderately positive Wassermann reaction in some cases of mononucleosis. A positive reaction to the diazo test has also been noted.

Pathology.—Since the disease is not fatal, there have been no complete pathologic studies made in cases in which there were no complicating disorders. Biopsies of glands have shown that lymphoid hyperplasia in itself is not diagnostic of mononucleosis.

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12. Davidsohn, I.: Serologic Diagnosis of Infectious Mononucleosis, J. A. M. A. **108**:289 (Jan. 23) 1937.

Diagnostic Problems.—As was noted earlier, the diagnosis in our cases was usually readily made and confirmed; we did, however, encounter a condition in triplets which left us in doubt as to whether we were dealing with mononucleosis. Until the etiology of the disease is known and demonstrable, in cases in which the clinical hematologic and serologic data do not conform to the classic picture it will be difficult or impossible to make the diagnosis, although it is likely that future studies will show variations from the classic type both in the blood picture and in the reaction to the heterophile agglutination test.

TABLE 2.—*Data from Cases of a Postmeasles Disorder in Triplets*

			Results of White Cell Counts						
Patient *	Clinical Data	Date	Leukocytes, per Cu. Mm.	Polymorphonuclears, %	Lymphocytes, %	Monocytes, %	Eosinophils, %	0	Heterophile Agglutination Titer
Marion P.	Measles developed on 12/12/38; 2 weeks later glands of neck, especially on left, swelled; patient did not look ill; tonsils large; lymph gland of left parotid size of olive; chain of glands in anterior cervical triangle on right slightly enlarged; axillary glands palpable; spleen not palpable	12/29	10,100	62	30	2	5	1	
		1/11	.....	..	..	..	..	..	1:64
		2/ 1	.....	54	32	8	6	..	
Margaret P.	No complaints; contracted measles 2 weeks before sisters (11/30/38); tonsils large; cervical glands enlarged; axillary glands palpable; spleen not enlarged	12/29	9,800	45	47	..	8	..	
		1/18/40	.....	..	..	..	..	..	1:64
		2/ 1/40	8,400	43	30	15	10	..	
Marilyn P.	Measles developed on 12/12/38; seen for a general check-up; tonsils a trifle large; cervical glands enlarged; later, axillary and inguinal glands enlarged; spleen not palpable	12/29	11,700	50	39	7	3	1	
		1/18	.....	..	..	..	..	..	1:64
		2/ 1	11,100	49	35	11	5	..	

* The patients were girls, 7¾ years old.

Data for the triplets are given in table 2. Margaret showed symptoms of measles on November 30; two weeks later her 2 sisters, Marion and Marilyn, became ill. When Marion and Marilyn had been convalescent for two weeks, the 3 girls came to the office for a routine postmeasles examination. Marion complained of swollen, tender glands. Examination showed that the lymph node over the left parotid was enlarged to the size of an olive, and the glands on both sides of the anterior cervical triangle were enlarged. The axillary glands were slightly enlarged, but the spleen was not palpable. There was no fever. The blood count was not remarkable, and the heterophile titer was only 1:64. We first thought that her 2 sisters might serve as controls in our observations on her, but examination revealed that they, too, had

TABLE 3.—*Data for Mononucleosis in Which There Was Involvement of the Central Nervous System*

Author	Sex and Age, Yr.	Date of Admission	Clinical Data	Results of Leukocyte Counts: Date	Leukocytes per Cu. Mm.	Polymorphonuclears, %	Lymphocytes, %	Monocytes, %	Eosinophils, %	Heterophile Agglutination Titer Date	Titer	Results of Examinations of the Spinal Fluid: Date	Total Cells per Cu. Mm.	Polymorphonuclears, %	Lymphocytes, %	Comment
A. Mononucleosis with Meningitis																
Thelander and Shaw (Miriam M.)	F 22	1/24/36	Chills; headache; nuchal rigidity; temperature ranged from 99 to 101 F., dropped to normal but on thirteenth hospital day rose to 101 F.; glands enlarged and spleen became palpable	1/24	15,050	75	21	2	1	....	.....	1/24	630	30	70	Gold curve normal
				.....	.....	..	..	..	..	....	.....	1/30	288	8	92	
				2/ 5	7,200	56	39	5	..	....	.....	2/ 6	194	12	88	
				2/10	9,250	32	55	7								
				2/11	15,650	30	61	9	..	....	.....	.....	...	..	..	Results of other examinations normal
				2/13	13,400	31	39	30	..	2/15	1:160	2/15	85	6	94	
				2/21	12,050	27	41	32	..	2/25	1:640					
				4/11	9,350	39	38	20	2	4/11	1:20	....	82	4	96	
B. Meningitis with the Blood Picture of Mononucleosis																
Thelander and Shaw (Patricia G.)	F 3½	5/18/40	Temperature 101 F.; drowsiness; pain but no stiffness in back of neck; convulsion; tonsils hyperemic; spleen not palpable; glands not enlarged	5/20	17,000	69	31	..	..	....	.....	5/20	40	63	37	Results of other examinations normal
				5/29	16,400	19	74	..	7	....	1:10					
				6/ 5	49,850	12	84	..	4	....	1:10					
				6/12	50,500	18	81	..	1		None					
				7/ 8	9,800	62	35	1	2							
Thelander and Shaw (Anita G.)	F 2½	5/22/40	Temperature 104.2 F.; drowsiness; anorexia; pain and slight stiffness in neck; twitching of muscles; rapid pulse; palpable cervical and "shotty" inguinal glands; spleen not palpable	5/22	45,700	16	81	1	..	....	.....	....	90	74	26	Results of other examinations normal
				5/23	39,400	14	83	3								
				5/29	36,900	12	82	..	6		±1:10					
				6/ 5	39,450	12	86	..	2		±1:20					
				7/ 8	9,350	46	43	..	11		None					
C. Cases Collected from the Literatuure																
Epstein and Dameshek [15]	M 19	12/5/29	Headache; blurring vision; photophobia, delirium; admitted to psychopathic service; temperature 108 F.; ptosis; generalized lymphadenopathy; palpable spleen	12/ 5	14,900	29	63	8	..	Not determined		.....	34	monocytes		
				12/11	25,700	32	50	8	..	.....		.....	28			
				12/18	26,900	55	32.5	12	0.5	.....		12/13	44			
												12/30	8			
Johansen [16]	M 28	5/25/30	Headache of 2 weeks' duration; fever; impaired memory; sluggishness; eyes closed; awkward speech; marked nuchal rigidity; temperature 39.6 C. (103.3 F.); later sore throat with exudate developed; glands and spleen not enlarged	5/28	11,000	22	76	2	..	Not determined		.....	16	monocytes		
				6/ 3	6,200	16	79	5								
				6/11	4,500	23	71	9	1							
				6/26	.....	60	38	1	7							

Pietzonka,[17] case 1	M 28	2/1/38	Eyes closed; slight opisthotonus and nuchal stiffness; tonsils injected; glands and spleen enlarged	....	21,400	11	86	3	..	....	1:64	....	29	..	..	Results of other examinations normal
Case 2	M 20	1/21/38	Swollen painful inguinal glands; later sore throat; Wassermann reaction negative; severe headache; slight exanthem; tonsils injected; glands and spleen enlarged	....	11,300	33	52	6	1	....	1:64	....	6	..	..	Results of other examinations normal
Case 3	M Adult	2/7/38	Headache; exudate in throat; glands enlarged and spleen enlarged later	....	18,900	18	80	1	1	....	1:64	....	9	..	..	Results of other examinations normal
Schmidt and Nyfeldt,[7] case 1	F 16	11/1/37	Severe infection of throat which had been diagnosed as peritonsillar abscess; ill 3 weeks; headache; temperature 37 to 39.6 C. (98.6 to 103.3 F.); adenitis; nuchal stiffness	11/ 1 11/ 6 11/ 8 11/15 11/26 1/ 3/38	16,400 7,400 6,400 ..... 7,400 4,800	30 25.5 32 .. 33.5 47	70 74.5 68 .. 66.5 53	.. ..	.. ..	11/5 11/11	1:128 1:64	....	26 monocytes 31 28 216 13		..	Listerellas recovered from cultures
Case 2	F 18	11/25/37	Severe infection of throat, had been diagnosed as peritonsillar abscess; headache; temperature 37.8 C. (100 F.); adenitis	..... 12/ 3 12/ 6 12/11 12/21	5,000 9,000 ..... 8,900 10,200	44 46 .. 49 64	56 54 .. 51 36	.. ..	.. ..	11/29 12/3	1:128 1:256	....	.. 10 70 lymphocytes 9	..	..	Listerellas recovered from cultures
Case 3	M 24	12/22/37	Ill 14 days; headache 7 days; pain in neck; temperature 38.5 C. (101.3 F.); slight involvement of throat early, more pronounced later; adenitis; no meningeal signs early	12/22 ..... 1/ 3	11,900 7,000	23 .. 28	77 .. 72	.. .. ..	.. .. ..	..... 12/27	..... 1:512	..... 12/28 1/ 3 1/11	.. 8 53 13	..	..	Listerellas recovered from cultures
Case 4	M 14	12/30/37	Infection of respiratory tract; edema of eyelids; diagnosis of frontal sinusitis made; temperature 38.8 C. (101.8 F.); enlarged tonsils; no signs referable to central nervous system; later headache	.... 1/13 1/31	16,200 7,200	24 30 34	76 70 66	.. .. ..	.. .. ..	1/15	1:64	.... 1/13	29 monocytes 115, mostly lymphocytes		..	Listerellas recovered from cultures
Case 5	F 23	6/9/38	Temperature 39 C. (102.2 F.); severe infection of throat diagnosed as peritonsillar abscess; no headache or signs referable to central nervous system; first lumbar puncture done because of experience in previous cases	....	..... 7,500 11,000	32 37 ..	68 63 ..	.. .. ..	.. .. ..	..... 1/12 1/15	..... None None	..... 1/15 1/19	18 26 12			

rather markedly enlarged cervical nodes and palpably enlarged axillary and inguinal glands. Their agglutination titer was also 1:64, and the blood picture was not conclusive. Mononucleosis has been reported as a complication of typhoid fever [13] and meningococcic disease,[14] and that the disease might follow measles, is, therefore, entirely possible. On the other hand, we did not know what a heterophile agglutination test for other patients during the postmeasles period might show, and since the titer was only 1:64, we did not feel justified in making the diagnosis of mononucleosis. Observations on the disorder of the triplets have been presented to show that confusing cases are encountered.

Treatment.—There is no specific treatment for the condition. Adequate rest and symptomatic therapy are indicated. In some cases there are prolonged malaise and fatigability, which should be met with much rest and supportive treatment.

Prognosis.—The prognosis is good.

OBSERVATIONS FROM CASES OF MONONUCLEOSIS IN WHICH THERE WAS INVOLVEMENT OF THE CENTRAL NERVOUS SYSTEM

Headache is not a rare symptom in infectious mononucleosis, but in most instances it is unaccompanied by any signs referable to the central nervous system. In communications from a number of physicians and in scattered reports in the literature lumbar punctures are stated to have revealed normal spinal fluid. There are, however, other reports in which studies of the spinal fluid have revealed pleocytosis. In table 3 are listed data for 3 of our cases of mononucleosis and for 10 cases collected from the literature in which there was involvement of the central nervous system. These cases have been divided into three groups: (*A*) 1 case of definite mononucleosis with meningitis, (*B*) 2 cases of meningitis in which there was marked lymphocytosis but the other clinical observations were not characteristic of mononucleosis and the heterophile agglutination titer was low, and (*C*) 10 cases in which the diagnosis was reported to be mononucleosis with serous meningitis or meningoencephalitis.

Miriam M. was referred to our service in the communicable disease ward by Dr. C. A. DeLancey with the diagnosis of meningitis of unknown cause. She had had slight fever and persistent, though moderate, headache for several days, but her nuchal stiffness had been so slight that a consultation was called before lumbar puncture was performed. The spinal fluid obtained at the first lumbar puncture

13. Schwartz, A. S., and Lindman, B.: Infectious Mononucleosis Complicating Typhoid Fever, Ann. Int. Med. **13**:895, 1939.

14. Stuart, C. A.; Welch, H.; Cunningham, J., and Burgess, A. M.: Infectious Mononucleosis: Further Studies, Arch. Int. Med. **58**:512 (Sept.) 1936.

showed 630 cells per cubic millimeter, most of which were lymphocytes, but in spite of this markedly abnormal condition her well-being belied the threat of any immediately serious illness. Her temperature dropped to normal after twenty-four hours, but a slight degree of nuchal stiffness remained, and two subsequent punctures within a period of twelve days revealed persistence of the pleocytosis. On the thirteenth day in the hospital she complained of soreness of the cervical glands and had a rise in temperature to 101 F. Examination revealed generalized, though slight, glandular hypertrophy and enlargement of the spleen. Daily blood studies thereafter showed a gradual increase in the percentage of lymphocytes. The reaction to the first heterophile agglutination test was positive (titer, 1 : 160) ; later the titer rose to 1 : 640. The spinal fluid at this time showed 85 cells per cubic millimeter. The fluid obtained by spinal puncture almost four months after onset still showed 82 cells per cubic millimeter. It will be noted from the table that in none of the other cases was there as marked or as persistent a pathologic condition of the spinal fluid as in this case.

The 2 sisters, Patricia and Anita G., were referred to our service by Dr. A. D. Sinclair. Their condition interested us greatly, but we were disappointed at being unable to confirm the diagnosis of mononucleosis by a positive reaction to the heterophile agglutination test. The illness of the first sister, aged 3½ years, began with fever, pain in the back of the neck and a convulsion. Little of importance was revealed by physical examination, and neither the lymph glands nor the spleen was palpably enlarged. Examination of the spinal fluid showed 40 lymphocytes per cubic millimeter. Her white cell count on admission was not remarkable, being 17,000 leukocytes per cubic millimeter of blood, with 69 per cent polymorphonuclears. A diagnosis of encephalitis of unknown cause was made. She was not lethargic and at no time appeared acutely ill. Four days later, however, her sister, aged 2½ years, became ill, with fever, pain in the neck and twitching of the muscles. Her temperature rose to 104.2 F. and she had slight nuchal stiffness. Examination of the spinal fluid showed 70 cells per cubic millimeter, chiefly lymphocytes. The blood count in this case aroused our interest. On admission, which was on the first day of her illness, examination showed 45,700 white cells per cubic millimeter, with 81 per cent lymphocytes. This result led us to repeat the blood studies made for her sister, with the results listed in table 3 (section B). Both girls had leukocyte counts of from 45,000 to 50,000 cells per cubic millimeter, with the percentage of polymorphonuclear leukocytes as low as 12. The heterophile titer, obtained three times, was only 1 : 10, with a possibly positive reaction with a dilution of 1 : 20 in one instance. In the absence of glandular hypertrophy and splenic enlargement and with such a low heterophile agglutination titer, we hesitated to make a diag-

nosis of mononucleosis in these 2 cases. The marked absolute lymphocytosis present in both cases, however, is so unusual that it must be of significance and must either point to a diagnosis of infectious mononucleosis or indicate a hitherto undescribed pathologic syndrome. We have seen in no other type of meningitis or encephalitis this kind of pathologic blood picture.

Section C of table 3 is a summary of data for cases collected from the literature in which serous meningitis or meningoencephalitis accompanied infectious mononucleosis. The first 2 cases were reported in 1931 almost simultaneously, 1 from the United States (Epstein and Dameshek [15]) and 1 from Denmark (Johansen [16]), before Paul and Bunnell [5] had published their report on the heterophile agglutination test. It may be noted that in Johansen's case there was no enlargement of the glands or spleen. The diagnosis in these 2 cases, and especially in the latter, is therefore as dubious as in our 2 cases (section B).

The symptom common to practically all of the cases in the literature was headache. Other symptoms were variable; in 1 case there were rather marked signs of encephalitis, with difficulty in speech, sluggishness and some mental confusion; in another case there was ptosis. In 2 cases of Pietzonka [17] the number of cells in the spinal fluid was within normal limits. Schmidt and Nyfeldt,[7] having had their interest aroused by the increased number of cells in the spinal fluid in their first case of mononucleosis, performed several lumbar punctures in their next 4 cases even though there were no symptoms or signs of involvement of the central nervous system. In case 2 they found an increase in cells from 8 to 29, with a count of 70 cells on one specimen; lumbar puncture revealed 53 cells at one time in case 3 and 415 cells in case 4. At no time were there marked signs referable to the central nervous system in any of these cases. Schmidt and Nyfeldt suggested that lumbar punctures should be done routinely in cases of mononucleosis, repeatedly if necessary, to determine the frequency of involvement of the central nervous system, and they expressed the belief that the data obtained thereby might be of value if sequelae occurred later. Johansen [16] suggested that some of the obscure encephalitides encountered may actually be mononucleosis. The same thought occurred to us when we saw our first case of mononucleosis with meningitis in 1936. However, we have had occasion to study a great many cases of encephalitis and benign lymphocytic meningitis the past two or three years because

15. Epstein, S. H., and Dameshek, W.: Involvement of the Central Nervous System in a Case of Glandular Fever, New England J. Med. **205**:1238, 1931.

16. Johansen, H. H.: Serous Meningitis and Infectious Mononucleosis, Acta med. Scandinav. **76**:269, 1931.

17. Pietzonka, H.: Meningitis serosa bei Pfeifferschem Drüsenfieber, Deutsches. Arch. f. klin. Med. **185**:153, 1939.

of increased prevalence of these diseases in this community, and aside from the 3 cases reported we have seen no cases in which the blood picture or the results of serologic tests suggested mononucleosis.

The exact pathologic changes in the nervous system are still obscure. It appears from this series of cases that there may be involvement of the brain, of the meninges or, possibly, of both. To date there has been no record of late sequelae. The adult patient, seen in 1936, is well, and the 2 girls recovered promptly and have had no sequelae to date.

SUMMARY

A summary of data from 6 cases of infectious mononucleosis, in which there were classic clinical symptoms, changes in the blood and heterophile agglutination titers, are presented. Characteristics of the disease are discussed.

Three cases of a disease which may have been mononucleosis but in which a diagnosis could not be made with any certainty are discussed.

Three new cases of infectious mononucleosis in which there was involvement of the central nervous system are reported, and a summary of observations in similar cases from the literature with a comment on the possible cause of the disease, are presented.

SERUM THERAPY OF TETANUS

WITH SPECIAL REFERENCE TO THE COURSE OF ANTITOXIN TITERS IN THE BLOOD AFTER TREATMENT WITH SPECIFIC SERUM *

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In another publication [1] I stated that tetanus antitoxin is best administered by the intravenous or the intramuscular route, in single doses of 40,000 to 60,000 units. In this paper attention is directed to a study of two lines of evidence which have been offered in support of the aforementioned method of treatment. The first consists of observations which indicate that tetanus toxin reaches the central nervous system directly by way of the blood stream, rather than by centripetal spread along the motor nerve trunks. The second reviews the observations made by me and by others which have shown that a single dose of 30,000 or more units of antitetanus serum, administered by the intravenous or the intramuscular route, is associated with an immunity which is adequate, both in level and in duration, to meet the indications imposed by a rational method of specific serotherapy.

PATHWAY BY WHICH TETANUS TOXIN REACHES THE NERVOUS SYSTEM

One school [2] contends that tetanus toxin is transported to the central nervous system by way of the peripheral nerve trunks, while the other [3]

Read before the Chicago Pediatric Society, Nov. 12, 1940.

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This investigation has been made with the assistance of a grant from the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association.

* Unless otherwise indicated, the units of antitoxin referred to in this paper are American units. According to the Pharmacopeia of the United States, the American unit is approximately twice the international unit.

1. Spaeth, R.: A Clinical Study of Tetanus, Am. J. Dis. Child. **60**:130-169 (July) 1940.

2. Meyer, H., and Ransom, F.: Untersuchungen über den Tetanus, Arch. f. exper. Path. u. Pharmakol. **49**:369-416, 1903. Marie, A., and Morax, V.: Recherches sur l'absorption de la toxine tétanique, Ann. Inst. Pasteur **16**:818-832, 1902. Teale, F. H., and Embleton, D.: The Paths of Spread of Bacterial Exotoxins, with Special Reference to Tetanus Toxin, J. Path. & Bact. **23**:50-68 (Oct.) 1919. Bromeis, H.: Die Wanderungsgeschwindigkeit des Tetanusgiftes in Tierkörper,

(Footnotes continued on next page)

presents convincing evidence in support of the theory that the toxin is conveyed directly to its destination by the arterial system. The presence of a barrier between the blood stream and the central nervous system is denied.[3c] Critical examination of the experimental data offered by these opposing groups favors the school which teaches that the blood stream is the main, if not the only, avenue by which tetanus toxin reaches the central nervous system.

Direct evidence in support of the theory that the toxin reaches its destination by way of the blood stream is represented by those studies which have demonstrated that specimens of blood obtained from animals or human beings with tetanus will exert a specific toxic effect. Although some investigators have claimed to have detected tetanus toxin in the blood of patients with various stages of the disease, others have reported only negative results.[3c] These conflicting reports may be understood, however, if attention is paid to six factors which may operate in the individual case. These factors may be enumerated as follows:

1. The ability of the tissues of animals given injections of tetanus toxin to fix the toxin in a nonrecoverable form. This feature varies markedly with the animal selected for study.[4] Once the tissues have

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Deutsche Ztschr. f. Chir. **250**:402-410, 1938. Robertson, H. E.: The Distribution of Tetanus Toxin in the Body, Am. J. M. Sc. **152**:31-48 (July) 1916.

3. (*a*) Abel, J. J.; Evans, E. A., Jr.; Hampil, B., and Lee, F. C.: Researches on Tetanus: II. The Toxin of the Bacillus Tetani Is Not Transported to the Central Nervous System by Any Component of the Peripheral Nerve Trunks, Bull. Johns Hopkins Hosp. **56**:84-114 (Feb.) 1935. (*b*) Abel, J. J.; Hampil, B., and Jonas, A. F., Jr.: Researches on Tetanus: III. Further Experiments to Prove That Tetanus Toxin Is Not Carried in Peripheral Nerves to the Central Nervous System, ibid. **56**:317-336 (June) 1935. (*c*) Abel, J. J.; Evans, E. A., Jr., and Hampil, B.: Researches on Tetanus: V. Distribution and Fate of Tetanus Toxin in the Body, ibid. **59**:307-391 (Nov.) 1936. (*d*) Abel, J. J.; Firor, W. M., and Chalian, W.: Researches on Tetanus: IX. Further Evidence to Show That Tetanus Toxin Is Not Carried to Central Neurons by Way of the Axis Cylinders of Motor Nerves, ibid. **63**:373-403 (Dec.) 1938. (*e*) Abel, J. J., and Chalian, W.: Researches on Tetanus: VIII. At What Point in the Course of Tetanus Does Antitetanic Serum Fail to Save Life? ibid. **62**:610-633 (June) 1938. (*f*) Abel, J. J.; Hampil, B.; Jonas, A. F., Jr., and Chalian, W.: Researches on Tetanus: VII. Time Required for Fixation of Fatal Quantity of Tetanus Toxin, ibid. **62**: 522-563 (May) 1938. (*g*) Abel, J. J.: On Poisons and Disease and Some Experiments with the Toxin of the Bacillus Tetani, Science **79**:121-129 (Feb. 9) 1934.

4. (*a*) Bolton, B. M., and Fisch, C.: An Estimate of the Amount of Toxin in the Blood of Horses Infected with Tetanus, Tr. A. Am. Physicians **17**:462-467, 1902. (*b*) Leyden, E., and Blumenthal, F.: Der Tetanus, in Nothnagel, H.: Specielle Pathologie und Therapie, 1900, vol. 5, pt. 2. (*c*) Abel, Evans and Hampil.[3c]

bound the tetanus toxin to the extent of their specific capacities, the unbound excess is recoverable in its active form from the blood and the lymph.[5] This difference may be outlined [3c] as follows:

Capacity of Tissues to Fix Tetanus Toxin	Recovery of Tetanus Toxin from Blood and Lymph	Typical Animals	Susceptibility to Tetanus
Negligible.....	Almost 100 per cent	Marsh turtle, alligator, fowls	Very slight
Moderate.....	The excess above 1 minimum lethal dose is stored in toto in the blood and lymph; if 1 minimum lethal dose or less is injected, toxin cannot be recovered	Guinea pig, sheep, horse, man	Pronounced
Pronounced....	The excess above 1 minimum lethal dose is stored only in part in the blood and lymph; hence, it may be impossible to recover free toxin even though the original dose was more than 1 minimum lethal dose	Dog, rabbit	Less than that of man, horse, guinea pig, and sheep

2. The amount of blood serum injected into the test animals. Abel and his associates [3c] and Leyden and Blumenthal [4b] have shown that this factor plays an important role in determining whether or not free toxin is detected. Leyden and Blumenthal placed emphasis on the necessity of using large amounts of blood serum from human beings with tetanus in order to demonstrate the specific toxic effects in laboratory animals.

3. The susceptibility of the test animal to tetanus toxin. This factor is of great significance because small amounts of toxin may not be demonstrable in specimens of toxiferous blood if animals relatively resistant to tetanus are employed for the bioassay. According to Yasayuma and Schobl,[6] the same amount of tetanus toxin is a single minimum lethal dose for 1 Gm. of mouse, 1.5 Gm. of rabbit, 2 Gm. of goat, 8 Gm. of guinea pig and 12 Gm. of horse. Beck [7] stated that the relative susceptibilities of the guinea pig and the mouse are in the ratio of 20:1. Bolton and Fisch [4a] calculated that the susceptibility of man is about 85 per cent as great as that of the guinea pig.

4. The amount of tetanus toxin which gains access to the body by natural or by artificial means. This factor determines the level reached both in the blood and in the lymph, as has been shown by controlled laboratory studies on animals.[8] If the amount of toxin originally present

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5. Abel, Evans and Hampil.[3c] Bolton and Fisch.[4a]

6. Yasayuma, K., and Schobl, O.: Free Toxin in the Blood During the Course of Tetanus Toxaemia, Philippine J. Sc. **32**:29-34 (Jan.) 1927.

7. Beck, M.: Experimentelle Untersuchungen über den Tetanus, Ztschr. f. Hyg. u. Infektionskr. **19**:427-449, 1895.

8. (*a*) Quadu, D.: Sulla presenza del velano tetanico nel sangue, Riforma med. **4**:182-187, 1894; cited by Abel, Evans, Hampil and Lee.[3a] (*b*) Knorr, A.: Experimentelle Untersuchungen über die Grenzen der Heilungsmöglichkeit des Tetanus durch Tetanusheilserum, Habilit.- Schr., Marburg, 1895; cited by Abel, Evans and Hampil.[3c] (*c*) Abel, Evans and Hampil.[3c] Leyden and Blumenthal.[4b] Yasayuma and Schobl.[6]

at the local focus does not provide a level in the blood above that needed to saturate the susceptible body tissues, toxic properties will not be demonstrable in specimens of blood serum injected into the test animals.[8c]

5. The time at which blood is drawn from the animal with tetanus. This factor influences the results of injecting the blood into test animals.[9] Abel and his associates [8c] placed considerable emphasis on the rapidity with which tetanus toxin is fixed in a

> non-recoverable and non-assayable form . . . by all the organs of the body that have an affinity for it, irrespective of their functional role or of the manner in which it influences them.

For given time intervals and in the presence of a local focus (natural or artificial) from which tetanus toxin continues to gain access to the blood stream, the presence or absence of toxin in the blood-lymph circulation will be determined both by the quantity available and by the specific attraction between the toxin and the various body tissues. After an initial rapid loss, caused by fixation in the tissues, a progressive rise in toxin titer may occur until a peak is reached. Beyond this point there may take place a definite decrease to a level at which toxic properties may or may not be demonstrable by available methods.[10] The time relation of the drop in the toxin titer and the onset of the physical signs of tetanus varies.[10]

6. The metabolic state of the animal with tetanus. Abel and his associates [8c] made the following remark:

> There is every reason to believe that the disappearance of the toxin from the blood is accelerated in the last hours of life . . . in consequence of the profound metabolic disturbances that have appeared by this time.

Frequently after tetanus toxin has been introduced into such animals as the horse,[11] the sheep,[12] the guinea pig [13] and the rabbit [8b] it may be

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9. (*a*) McClintock, T. C., and Hutchings, W. H.: The Treatment of Tetanus, J. Infect. Dis. **13**:309-320 (Sept.) 1913. (*b*) Abel, Evans and Hampil.[8c] Bolton and Fisch.[4a] Leyden and Blumenthal.[4b]

10. Abel, Evans and Hampil.[8c] Bolton and Fisch.[4a] McClintock and Hutchings.[9a]

11. (*a*) Madsen, T.: Tetanusgift in Serum eines Diphtherieimmunisierten Pferdes, 5 Tage vor dem Ausbruch von Tetanus, Centralbl. f. Bakt. **46**:276-278, 1908. (*b*) Permin, C.: Experimentelle und klinische Untersuchungen über die Pathogenese und Therapie des Starrkrampfes, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **27**:1-72, 1914. (*c*) Siegert, F.: Tetanus mid todlichem Ausgang in Folge von Diphtherieheilserum-Injektionen in Italien, München. med. Wchnschr. **48**: 166-167, 1901; cited by Abel, Evans and Hampil.[8c] (*d*) Schutz: Versuche zur Immunisierung von Pferden und Schafen gegen Tetanus, Ztschr. f. Hyg. u. Infektionskr. **12**:45-57, 1892. (*e*) Abel, Evans and Hampil.[8c] Bolton and Fisch.[4a]

12. Abel, Evans and Hampil.[8c] McClintock and Hutchings.[9a]

(Footnotes continued on next page)

demonstrated in samples of blood obtained either during life or after death. On two occasions [14] a number of deaths from tetanus have followed the injection of diphtheria antitoxin obtained from horses before the onset of symptoms of tetanus.[15] In one laboratory [11a] specimens of blood secured from a horse being immunized against diphtheria caused tetanus when injected into susceptible laboratory animals. The samples of blood had been obtained five days before the horses showed physical signs of tetanus. McClintock and Hutchings [9a] detected tetanus toxin in the blood of sheep which had been artificially infected with spores as long as four days before the onset of the disease. A number of writers [16] have reported that tetanus toxin was present in specimens of blood obtained from human beings with the disease. Yasayuma and Schobl [6] induced fatal tetanus in a guinea pig by the subcutaneous injection of blood secured several days before death from a child who had tetanus of about two months' duration. Permin [11b] reported that tetanus toxin was present in specimens of blood obtained from 2 patients who died, but he was unable to detect it in those secured from 2 patients who recovered. My own results [17] are inconclusive.

It seems reasonable to suppose that when the blood is heavily laden with tetanus toxin some toxin will find its way into the spinal fluid or the urine.[3c] Although there are isolated, but not too convincing, reports in the literature on the detection of tetanus toxin in the spinal fluid of human beings,[18] results of attempts to detect the toxin in the spinal fluid in general have been negative.[3c] Similar attempts to isolate tetanus toxin from the urine of patients with tetanus have yielded varying results.[19]

Indirect evidence may be adduced in favor of the theory which subscribes to the hematogenous transport of tetanus toxin to the central

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13. Francis, E.: Experiments on Tetanus, Hygienic Laboratory Bulletin 95, United States Treasury Department, Public Health Service, 1914. Pestana, C.: De la diffusion du poison du tetanos dans l'organisme, Compt. rend. Soc. de biol. **43**:511-513, 1891. (*c*) Abel, Evans and Hampil.[3c] Yasayuma and Schobl.[6] Beck.[7] Quadu.[8a]

14. Bolton and Fisch.[4a] Siegert.[11c]

15. This was in the early days of serum manufacture, before the introduction of the safety devices which are now employed.

16. (*a*) Bruschettini, (*b*) Faber, (*c*) Blumenthal, (*d*) Stern and (*e*) Stintzing, all cited by Permin.[11b] (*f*) Yasayuma and Schobl.[6] Permin.[11b]

17. Spaeth, R.: Unpublished data.

18. Permin.[11b] Stintzing.[16e]

19. Brunner, C.: Zur Kenntnis des Tetanusgiftes, Ztschr. f. klin. Med. **32**: 207-214, 1897. Kartulis, S.: Untersuchungen über das Verhalten des Tetanusgiftes im Körper, Inaug. Dissert., Berlin, G. Schade, 1892. These references were cited in the article by Abel, Evans and Hampil.[3c] Leyden and Blumenthal.[4b] Abel, Evans and Hampil.[3c]

nervous system. The first form of evidence may be presented as follows: Other conditions being equal, the site of the injury does not influence the length of the incubation period. If tetanus toxin reaches the central nervous system mainly by way of the blood stream, rather than by spread along the motor nerves, one would anticipate that the quantity of toxin present at the focus of infection, rather than the length of the motor nerve supplying the diseased part, would determine the length of the incubation period. In experimental animals the dose of toxin does influence directly the length of the incubation period.[7] However, in human beings with tetanus the amounts of toxin engendered at the points of injury apparently vary considerably. This is suggested by the wide range of incubation periods which have been observed in cases of the disease in human beings. Obviously, such a situation makes it difficult to classify patients accurately in terms of the degree of intoxication. However, for general purposes, such a classification may be secured by separate consideration of the cases with fatal termination and those in which recovery ensued (table 1).[20]

The slightly longer average incubation period for the cases in which the lower extremity was the site of the injury is explained by the inclusion of 2 with unusually long incubation periods, one of one hundred and the other of eighty days. If this fact is taken into consideration, it may be stated that the analysis failed to reveal a correlation between the length of the motor nerve and the length of the incubation period. Such a conclusion tends to contradict the teaching [21] that the greater the distance of the local focus from the central nervous system, the longer is the incubation period.

20. The points of the body used in table 1 were selected because there are significant differences in the lengths of the motor nerves supplying these parts. The interior of the abdomen was chosen as a separate site because fatalities in the cases in which the lesion was located at that site are not necessarily related to the severity of the intoxication. Peritonitis, postoperative complications and other conditions might increase the death rate in this group of cases. Furthermore, the more rapid absorption of toxin might shorten the incubation period. Because specific serotherapy could obscure any classification based on the recovery or the death of the patient, the data were originally analyzed according to whether treatment with antitetanus serum had been given. Among the cases with fatal termination in which serum was not given, there were only 7 in which the lesion was not on the extremities and among those in which recovery ensued only 4. The average incubation periods for cases in which the lesion was located on the upper or the lower extremities were essentially the same whether antitoxin had or had not been administered. On the basis of these observations, classification in terms of specific serum therapy has not been considered necessary.

21. (*a*) Grinker, R. R.: Neurology, Springfield, Ill., Charles C. Thomas, Publisher, 1934. (*b*) Kairinschtis, W.: Neue statistische Daten und Gesetzmassigkeiten aus der Pathologie des Tetanus, Ztschr. f. Hyg. u. Infektionskr. **95**:220-232, 1933.

If tetanus toxin reaches the central nervous system by way of the blood stream, rather than by diffusion along the motor nerves supplying the diseased part, there should be no consistent relation between the distance of the local focus from the central nervous system and the mortality rate (tables 2 and 3).[22] The analysis indicates that the site of infection and the mortality rate are independent of each other. It is of note that the patients whose lesions were close to the central nervous system (region of the head and neck), had the lowest mortality rate and those with foci of infection within the abdomen, on the trunk or on the genitals had the highest rate. The vast majority of the patients with

TABLE 1.—*Site of Infection and Average Incubation Period in 847 Cases of Tetanus* *

Site of Infection	Cases in Which Patient Recovered		Cases in Which Patient Died		All Cases	
	No.	Average Incubation Period, Days	No.	Average Incubation Period, Days	No.	Average Incubation Period, Days
Lower extremity	141	12.6†	266	9.5‡	407	10.6
Upper extremity	135	11.7	195	8.4	330	9.7
Head and neck	38	10.4	29	9.5	67	9.6
Interior of abdomen	4	9.5	20	8.1	24	8.3
Trunk and genitalia	3	9.7	16	6.8	19	7.3

* The sources of the cases are as follows: 180 cases from Anders and Morgan (A Preliminary Report of a Statistical Study, J. A. M. A. **45**: 314-322 [July 29] 1905); 213 cases from Moschcowitz (Tetanus: A Study of the Nature, Excitant, Lesions, Symptomatology, and Treatment of the Disease, with a Critical Summary of the Results of Serum Therapy, Ann. Surg. **32**: 219-250, 416-445 and 575-601, 1900); 31 cases from Miller and Rogers (Present Status of Tetanus, with Special Regard to Treatment, J. A. M. A. **104**: 186-191 [Jan. 19] 1935); 225 cases from Kairinschtis [21b] (data from table 4 of the article are included, except for those cases in which the incubation period was longer than seventeen days); 81 cases from the University Hospitals, Iowa City (1917-1935); 157 cases from Cook County Hospital, Chicago (1912-1933), and 10 cases from Children's Memorial Hospital, Chicago (1912-1933), made available for study by Dr. Joseph Brennemann.

† One incubation period of one hundred days was included in computing the average.

‡ One incubation period of eighty days was included in computing the average.

lesions within the abdomen were handicapped by such conditions as peritonitis, puerperal sepsis, septic abortion and unfavorable sequelae of surgical procedures on the abdomen. Obviously, the risks attending these conditions, even in the absence of tetanus, could explain the higher

22. In tables 2 and 3 the same five points of the body have been used as in table 1. In table 2 a separate group of cases is considered, those in which the point of infection was either unknown or not described. The analysis has been controlled by considering both separately and together the data for cases in which antitoxin therapy was employed and those for cases in which it was not used. Such a method of analysis is indicated in view of the influence of serum treatment on the mortality rate, as revealed both by table 2 and by table 3. Since the incubation period is ordinarily longer in cases of the milder forms of tetanus, the analysis has been further controlled by considering the average incubation periods for each group of patients (table 3).

mortality in this group of patients. A large number of the patients with lesions on the trunk had tetanus neonatorum, with the usual primary focus in the infected umbilical stump. The relatively low resistance

TABLE 2.—*Site of Infection and Mortality in 1,028 Cases of Tetanus* *

Site of Infection	Cases in Which Antitoxin Was Administered			Cases in Which Antitoxin Was Not Administered			All Cases		
	No.	No. of Deaths	Mortality Rate, per Cent	No.	No. of Deaths	Mortality Rate, per Cent	No.	No. of Deaths	Mortality Rate, per Cent
Lower extremity	448	235	52.45	55	48	87.27	503	283	56.28
Upper extremity	277	147	53.05	43	34	79.07	320	181	56.56
Region of head and neck	73	30	36.58	10	5	50.0	83	35	42.16
Trunk, including genitalia	24	18	75.0	4	4	100.0	28	22	78.57
Interior of abdomen	29	24	82.75	4	2	50.0	33	26	78.78
Unknown or not stated	53	20	37.73	8	6	75.0	61	26	46.62
Total	904	474	52.43	124	99	79.83	1,028	573	55.74

* The sources of the cases are as follows: 213 cases from Anders and Morgan; 287 cases from Moschcowitz; 30 cases from Miller and Rogers; 39 cases from the University Hospitals, Iowa City (1917-1935); 114 cases from Vener, Bower and McKillop (Clinical Tetanus: A Study of One Hundred and Thirty-One Cases, California & West. Med. 39 : 309-312 [Nov.]; 374-380 [Dec.] 1933); 157 cases from Graves (Tetanus in New Orleans, Ann. Surg. 92 : 1075-1086 [Nov.] 1930); 195 cases from Cook County Hospital, Chicago (1922-1933), and 13 cases from Children's Memorial Hospital, Chicago (1912-1933), made available for study by Dr. Joseph Brennemann.

TABLE 3.—*Site of Infection and Mortality in 620 Cases of Tetanus* *

Site of Infection	Cases in Which Antitoxin Was Given				Cases in Which Antitoxin Was Not Given				All Cases			
	Number	Incubation Period, Days	No. of Deaths	Mortality Rate, per Cent	Number	Incubation Period, Days	No. of Deaths	Mortality Rate, per Cent	Number	Incubation Period, Days	No. of Deaths	Mortality Rate, per Cent
Lower extremity	219	10.6	113	51.6	49	10.6	43	87.8	268	10.6	156	58.2
Upper extremity	204	9.9	100	49.0	40	8.4	32	80.0	244	9.6	132	54.1
Head and neck	55	10.2	25	47.3	8	6.1	4	50.0	63	9.7	29	46.0
Trunk and genitalia	17	6.9	14	82.4	2	6.0	2	100.0	19	6.8	16	84.2
Interior of abdomen	23	8.3	19	82.6	3	21.0	1	33.3	26	9.7	20	76.9
Total	518	10.0	271	52.4	102	8.6	82	80.4	620	9.9	353	56.9

* The sources of the cases are as follows: 182 cases from Anders and Morgan; 213 cases from Moschcowitz; 27 cases from Miller and Rogers; 31 cases from the University Hospitals, Iowa City (1917-1935); 157 cases from Cook County Hospital, Chicago (1922-1933), and 10 cases from Children's Memorial Hospital, Chicago (1912-1933), made available for study by Dr. Joseph Brennemann.

characteristic of the newborn period, the massiveness of intoxication and nonspecific complications (starvation, diarrhea and dehydration) probably contributed to the heavy death toll in this group of patients.

The variety of symptoms [23] in cases of tetanus in which the lesions are essentially similar can be explained more adequately by the theory that tetanus toxin is brought directly to the central nervous system by the blood stream than by the teaching that the toxin spreads centripetally along the motor nerves. If the motor nerves served as the main avenues of travel, one would expect a rather regular occurrence of classic descending tetanus, characterized by the early appearance of spasticity in the cephalic region and its relatively late onset in the extremities.[24] The many instances which might be cited in which such a sequence of signs did not appear [23] speak against the acceptance of such a theory. Abel and Hampil [25] have stressed this fact as follows:

> Tetanus is a disease of such varied symptoms, quite unpredictable in respect to the relative order of their appearance, that it is never safe to make positive assertions as to the rarity of this or that symptom or the relative order in which the symptoms occur.

COURSE OF THE BLOOD TITER AFTER INJECTION OF ANTITOXIN

In 1895 Beck [7] found high antitoxin titers, both during life and after death, in the specimens of blood obtained from a patient with tetanus who died on the fifth day of the disease despite repeated intravenous injections of specific serum. Dean [26] determined the antitoxin titers, at various intervals after the injection of antitetanus serum, of 8 patients, 7 of whom had received single intravenous doses of approximately 30,000 American units. His data, which are summarized in table 4, reveal that as late as thirty-nine days after the serum treatment appreciable quantities of antitoxin were still present in the circulating blood.

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23. (*a*) Bruce, D.: Tetanus: Analysis of 1,458 Cases Which Occurred in Home Military Hospitals During Years 1914-1918, J. Hyg. **19**:1-32 (July) 1920. (*b*) Paterson, A. E.: Tetanus: Its Diagnosis and Treatment with a Summary of Twenty-Six Consecutive Cases, M. J. Australia **1**:832-834 (June 28) 1930. (*c*) Abel, J. J., and Hampil, B.: Researches on Tetanus: IV. Some Historical Notes on Tetanus and Commentaries Thereon, Bull. Johns Hopkins Hosp. **58**:343-376 (Dec.) 1935. (*d*) Spaeth.[1]

24. According to this theory (Permin,[11b] p. 31) toxin is carried into the blood stream, from which it is picked up by the endings of the motor nerves, along which it then travels, symmetrically and bilaterally, to reach the medullary and spinal nuclei which innervate the various muscles of the body. Such a process would necessitate a definite correlation of the relative time of onset of local muscle spasm with the length of the motor nerve supplying the focus of infection. Since the motor nerves of the body increase in length caudad trismus would appear first, followed by spasticity of the muscles of the neck, the trunk (thorax and abdomen) and the lower extremities in the order named.

25. Abel and Hampil,[23c] p. 359.

26. Dean, H. R.: Report on Twenty-Five Cases of Tetanus to the Medical Research Committee, Lancet **1**:673-680 (May 5) 1917.

Cole and Spooner [27] observed that twenty-eight to thirty-two days after a single intravenous injection of 200,000 international units of tetanus antitoxin the blood serum of 3 patients contained 1.25 to 3.33 units of the antitoxin per cubic centimeter. In another patient, 0.1 unit per cubic centimeter was detected in the blood serum as late as sixty-three days after the intravenous administration of 200,000 international units. In table 5 the data of Cole and Spooner are summarized.

TABLE 4.—*Antitoxin Titers in 7 Cases of Tetanus* *

Case No.	Units of Antitoxin in Single Intravenous Injection	Interval Between Injection of Antitoxin and Collection of Blood for Titration, Days	No. of Cc. of Toxin Neutralized by 1 Cc. of Patient's Serum	No. of Cc. of Toxin Fatal to Guinea Pig †	No. of Lethal Doses of Toxin † Neutralized by 1 Cc. of Patient's Serum
4	31,500‡	6	0.05	0.0005	100
		17	0.01	0.0010	10
11	30,000	8	1.00	0.0010	1,000
25	30,000	19	0.02	0.0005	40
24	30,000	20	0.02	0.0005	40
23	30,000	25	0.40	0.0030	133
20	30,000	30	0.04	0.0030	13
15	30,000	39	0.10	0.0020	50

* Data are from Dean.[28] Two titrations were performed in case 4. Case 18 was excluded because a second dose of serum was given four days after the first injection. All of the patients recovered.

† The control animals, which died six to eight days after the injection of toxin, weighed approximately the same as those used for the titration. Their weights were: in case 4, 500 Gm.; in cases 11 and 15, 650 to 850 Gm., and in cases 20, 23, 24 and 25, not stated.

‡ In this case 1,500 units was injected subcutaneously the day before 30,000 units was injected intravenously.

TABLE 5.—*Course of Blood Titers in 4 Cases of Tetanus After Intravenous Injection of Antitoxin* *

Case No.	Interval Between Injection of Antitoxin and Collection of Blood, Days																		
	2	3	4	5	8	9	10	12	13	14	15	16	18	22	24	28	32	41	63
1	—	25	—	25	12.5	10	—	5	—	—	5	—	—	—	1.25	—	3.33	—	—
2	—	—	20	—	—	—	—	—	—	5	—	—	—	—	—	1.25	—	—	—
3	40	—	—	—	—	—	14.3	—	—	—	—	6.7	6.7	—	—	—	2.5	—	—
4	—	—	—	—	—	—	—	—	3.33	—	—	—	—	0.33	—	—	—	0.1	0.1

* The data are from Cole and Spooner.[27] A single injection of 200,000 international units was given. The titers are expressed in international units per cubic centimeter of blood serum.

Sohier and Jude [28] found that the antitoxin titer of the blood of a patient with tetanus who had received 1,254,000 international units of antitoxin over a period of eleven days, practically the entire amount by the intramuscular and subcutaneous routes, was 30 to 50 units per cubic

27. Cole, L., and Spooner, E. T. C.: The Treatment of Tetanus, with Observations on the Fate of Injected Antitoxin, Quart. J. Med. **4**:295-319 (July) 1935.

28. Sohier, R., and Jude, A.: Recherches sur le sort de l'antitoxine chez un tétanique traité par la sérothérapie spécifique associée à l'anesthésie générale, Bull. et mém. Soc. méd. d. hôp. de Paris **54**:80-85 (Jan. 24) 1938.

centimeter on the sixth day after the termination of specific serotherapy, 3 to 30 units on the fifteenth to the thirty-ninth day and between 1/100 and 1/30 unit on the eighty-sixth to the one hundred and sixth day.

Similar studies [29] conducted on the blood serum of patients with diphtheria who were given specific serotherapy have shown that considerable quantities of antitoxin are present as late as one or two months after the termination of specific treatment. Madsen [29b] found that four weeks after the injection of 40,000 to 280,000 units of diphtheria antitoxin considerable blood titers were present, an observation which indicates that the antitoxin immunity is of longer duration than the period of three to four weeks which is commonly accepted. Madsen observed that in no case did the antitoxin totally disappear during an observation period of five to six (in 1 case, nine) weeks.

In this report I shall present the results of the titrations carried out on 26 specimens of blood obtained from 14 patients with tetanus who had received specific serotherapy, from 4 patients given prophylactic doses of antitoxin and from 1 given an injection of antitetanus serum for purely investigative purposes.

METHODS

Blood was drawn from the median cubital or other accessible vein. It was allowed to stand until clotting had occurred. The clot was separated from the side of the tube by means of a sterile wire. Clear serum was obtained by centrifuging. Five cubic centimeters of the clear serum was pipetted into a sterile centrifuge or short test tube. With sterile distilled water as the diluent, seven different dilutions were prepared from 2 cc. of this clear serum, as follows: 1:25, 1:125, 1:250, 1:625, 1:1,250, 1:2,500 and 1:5,000.

Approximately 10 mg. of potent tetanus toxin [30] was weighed on a balance sensitive to at least 0.1 mg. The toxin was dissolved in 100 cc. of sterile distilled water, added in 2 cc. amounts directly to the material in the weighing glass, by gently agitating the mixture with a smooth glass stirring rod, and the resulting solution was carefully transferred to a 100 cc. graduated, glass-stoppered flask. This process was repeated at least fifteen times to make certain that all the toxin was removed from the weighing glass. The solution in the flask was brought up to the 100 cc. mark. The flask was agitated for about five minutes to make the solution homogeneous. From this solution were prepared seven

29. (*a*) Ramon, G.; Debré, R., and Bernard, J.: Sur les variations de la teneur en antitoxine dans la sérum des sujets atteints de diphtérie et soumis à la sérothérapie spécifique, Compt. rend. Soc. de biol. **114**:1091-1094, 1933. (*b*) Madsen, E.: The Course of the Passive Immunity After Treatment with Anti-Diphtheria Horse Serum in Rabbits and in Man (Preliminary Report), Acta path. et microbiol. Scandinav. **13**:103-116, 1936.

30. The toxin used in this study was obtained from the National Institute of Public Health, Washington, D. C., through Dr. George W. McCoy. The L + dose (test dose) was 0.00068 Gm. (as determined in the Washington laboratories). Because the titrations were determined over a period of about two years, four different specimens of dried toxin were employed in the course of this study. However, the L + values were essentially the same for all batches of the toxin.

additional dilutions, which contained 0.001, 0.002, 0.003, 0.004, 0.005, 0.01 and 0.04 mg. of toxin per cubic centimeter.

Because accidental deaths of a purely environmental nature sometimes occurred, duplicate sets of animals were used for the titrations and as controls.

Two series of nine short test tubes each were set up in a rack. To each of the first seven tubes of each series was added 1 cc. of one of the dilutions of the serum [31] to be tested, in the order of increasing concentration. To the last two tubes of each series 0.4 and 1 cc., respectively, of the undiluted serum were added.

To each of these tubes was added a volume of toxin solution corresponding to 0.04 mg. of the dried toxin. However, to the last tube of each series (containing 1 cc. of undiluted serum) only 0.01 mg. of toxin was added. Each of these solutions was gently rotated to insure thorough mixing. They were then allowed to stand at room temperature for one hour.

TABLE 6.—*Determination of the Neutralizing Power of Human Blood Serum* *

Weight of Animal, Gm.	Tetanus Toxin Injected, Mg.	Human Blood Serum Injected		Results	Mg. of Toxin Neutralized by 1 Cc. of Serum †
		Dilution	Volume, Cc.		
18	0.04	1:5,000	1.0	Death within 24 hr.	200
17	0.04	1:2,500	1.0	Death within 24 hr.	100
17	0.04	1:1,250	1.0	Death within 24 hr.	50
18	0.04	1:625	1.0	Death within 24 hr.	25
16	0.04	1:250	1.0	Death within 24 hr.	10
17	0.04	1:125	1.0	Death in 48 hr.	5
18	0.04	1:25	1.0	Tetanus did not appear	1
18	0.04	....	0.4	Tetanus did not appear	0.1
19	0.01	....	1.0	Tetanus did not appear	0.01
			Controls		
19	0.04	....	...	Death within 24 hr.	...
18	0.04	....	...	Death within 24 hr.	...
23	0.01	....	...	Death in 48 hr.	...
16	0.01	....	...	Death in 48 hr.	...
20	0.004	....	...	Death in 72 hr.	...
19	0.004	....	...	Death in 72 hr.	...
20	0.003	....	...	Death in 72 hr.	...
15	0.003	....	...	Death in 72 hr.	...
17	0.002	....	...	Death in 72 hr.	...
15	0.002	....	...	Death in 72 hr.	...
20	0.001	....	...	Death in 6 days	...
20	0.001	....	...	Death in 7 days	...

* Constant weights of tetanus toxin were mixed with various dilutions of blood serum, allowed to stand at room temperature for one hour and the solutions then injected intraperitoneally into white mice. The final titer obtained in this experiment was: One cubic centimeter of serum neutralizes 1 to 5 mg. of toxin.

† This value was calculated as follows: milligrams of toxin used $\times \frac{\text{dilution of serum}}{\text{volume of serum}}$

At the end of one hour the toxin-serum solutions, in the order of increasing concentrations of the blood serum, were injected intraperitoneally into white mice weighing approximately 15 Gm. With a separate syringe, the control animals were given intraperitoneal injections of the toxin in the order of increasing amounts.

The data for a titration are given in table 6.

31. After the blood specimens had been centrifuged, the clear supernatant serums were kept in sterile containers under standard conditions of refrigeration. Before the individual titrations were carried out, smears of the serums were stained with methylene blue (methylthionine chloride U. S. P.) to detect any bacterial growth. In no instance was microbic contamination demonstrable by this technic.

The animals were observed every six to twelve hours and the necessary notations made. Observations were continued for six or seven days, at the end of which time the animals were killed by means of ether inhalations. The amount of toxin which in six days killed a white mouse weighing 15 Gm. was arbitrarily considered the minimum lethal dose.

The results of each titration were expressed in terms of milligrams of toxin neutralized by 1 cc. of blood serum. These figures may be interpreted in terms of the minimum lethal dose on the basis of the observations made on the control animals. Instead of fixed values definite ranges were used to express the titers,

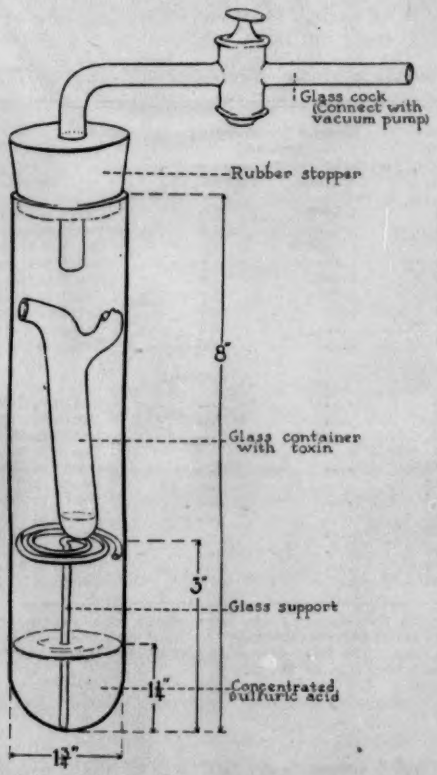

Fig. 1.—Apparatus in which toxin was kept.

as may be noted in table 7. This method of designation has been considered satisfactory for the purposes of this study.

The presence of antitoxin could be detected at the end of twenty-four hours by examining and comparing the blood of the animals given injections of the serum-toxin mixtures and of the controls which had received toxin. To determine the exact level of the titer required six days of observation, however, because it was necessary to determine the minimum lethal dose of the toxin employed.

The toxin used in the titrations was kept over concentrated sulfuric acid under a partial vacuum in the container illustrated in figure 1.

The mice were fed a diet of bread, water, lettuce and carrots. Sixteen animals were kept in an average-sized cage. All dead animals were removed as soon

as possible because of the apparent "cannibalistic tendencies" of their live mates. By the use of carbolfuchsin and gentian violet, singly and in combination, on three different sites (head, back and rump), sixteen different color combinations, lasting and clearly distinguishable, were obtained for purposes of identification.

In a footnote to table 7 reference is made to the number of the titration method employed. This has been necessary because various technics were tried out before method 1 was evolved. As already noted, the final procedure used was method 1 (table 6). The technic of method 1 *A* differed from that of method 1 in that the serum-toxin solutions were injected into the thighs of guinea pigs instead of into the abdominal cavities of white mice. Method 1 *B* differed from 1 *A* in that the weights of toxin employed were either less than or greater than 0.04 mg. Method 2, the first employed, was based on the use of constant volumes of undiluted serum and various weights of toxin. Since it would serve no useful end to include descriptions of all the variations of the technic finally used, only method 1 is described in this report.

RESULTS

In table 7 the results of the titrations are presented, together with the essential clinical and laboratory data. The doses of serum are those given on the containers in which the therapeutic serums were supplied. The ages of the specimens of human blood serum are noted because delay in performing the titrations was occasioned at times by extraneous circumstances.

Table 8 gives the results of the injection of toxin into the control animals. As already stated,[80] four different specimens of dried toxin were used during the two year period over which this study was conducted. The test doses (L + values) were essentially the same for all four specimens of toxin. The minimum lethal dose was not determined in all of the experiments, and various amounts of toxin were employed in the different titrations. This lack of uniformity was occasioned by the adoption of various technics as the study progressed. Guinea pigs were employed in the earlier titrations (cases 1 to 11) and white mice in the rest (cases 12 to 19). However, the use of two different types of animal does not prevent a general comparison of the titration values, for it requires approximately the same amount of toxin to cause fatal tetanus in a white mouse weighing 15 Gm. as in a guinea pig weighing about 200 Gm.

Table 8 shows that all control animals given injections of toxin of 0.01 mg. or more died of tetanus. However, smaller amounts yielded various results: One-thousandth milligram killed 2 white mice (cases 12 and 18) and 0.0024 mg. 2 guinea pigs (case 2), whereas a significantly greater quantity, 0.004 mg., failed to kill 2 white mice (case 19). However, it is to be emphasized that the toxin was demonstrated to be highly lethal for all except 2 control animals. This observation is emphasized primarily because of the results noted in the controls for case 19. In

TABLE 7.—*Clinical and Laboratory Data for 19 Cases**

Case No.	Age, Yr.	Length of Hospitalization, Days	Symptoms	Incubation Period, Days	Clinical Outcome	Antitoxin Therapy: Day of Disease When Serum Was First Given	Antitoxin Therapy: Total Dose, Thousands of Units	Antitoxin Therapy: Routes	Antitoxin Therapy: No. of Days	Interval, Days, Between First Injection of Antitoxin and Drawing of Blood	Age of Specimen of Human Blood Serum, Days	Mg. of Tetanus Toxin Neutralized by 1 Cc. of Human Blood Serum †
1	35	.....	.....	..	Recovered	...	30	Intravenous	1	14	4 hr.	6.2 - 12.5
2	4	5/17- 6/18/33 (32)	Severe	20	Recovered	2d	60	Intravenous	1	6	4 hr.	112.0
										24	2 hr.	20.0 - 30.0
										30	2 hr.	20.0 - 25.0
3	50	?	Moderate	?	Recovered	?	66	Intravenous; intramuscular; intrathecal	2	32	7	0.1 - 1.0
4	33	6/27- 7/24/34 (27)	Mild	?	Recovered	6th	50	Intravenous	1	21	17	0.1 - 1.0
5	4	.....	.....	..	Recovered	...	5	Intramuscular	1	19	9	0.01 - 0.1
6	6	6/17- 6/23/34 (6)	Severe	?	Died	1st	60	Intravenous	1	7	41	25.0 - 50.0
7	12	6/ 9- 7/22/34 (43)	Severe	6	Recovered	1st	60	Intravenous	1	21	35	1.0 - 5.0
										35	25	0.1 - 1.0
										42	14	0.1 - 1.0
8	20	7/28- 8/19/33 (32)	Severe	3	Recovered	3d	85	Intravenous; intramuscular	4	21	21	1.0 - 5.0
										35	7	0.1 - 1.0
9	5	7/21- 8/ 3/33 (13)	Mild	?	Recovered	6th	20	Intravenous	1	8	28	25.0 - 50.0
10	3	7/ 6- 8/ 1/33 (26)	Severe	3	Recovered	2d	80	Intravenous	1	25	27	25.0 - 50.0
11	35	7/24- 8/ 3/33 (10)	Severe	5	Died	3d	60	Intravenous	1	10	24	10.0 - 25.0
12	5	.....	.....	..	Recovered	...	1.5	Intramuscular	1	26	28	0
13	65	.....	.....	..	Recovered	...	5	Intramuscular	1	29	29	0
14	35	.....	.....	..	Recovered	...	5	Intramuscular	1	26	29	0.01 - 0.1
15	8	9/21-10/10/34 (19)	Severe	10	Recovered	3d	60	Intravenous	1	18	24	10.0 - 25.0
										21	60	5.0 - 10.0
										35	1	0.01 - 0.1
16	10	10/ 4-10/18/34 (14)	Mild	?	Recovered	9th	45	Intramuscular	1	30	2	1.0 - 5.0
17	12	10/28-11/18/34 (31)	Severe	14	Recovered	2d	100	Intravenous	1	28	28	10.0 - 25.0
18	5	11/25-12/15/34 (30)	Severe	?	Recovered	3d	100	Intravenous	1	28	7	1.0 - 5.0
19	8	8/24- 9/21/34 (28)	Severe	9	Recovered	2d	100	Intravenous	1	28	28	10.0 - 25.0

* All of the patients were white, and all were males except in cases 7, 8, 11, 12, 13, 15, 17 and 18. All of the patients had tetanus except those in case 1 (a man with a neurologic disorder who was given foreign protein therapy with tetanus antitoxin) and cases 5, 12, 13 and 14 (patients given antitoxin for prophylaxis against tetanus).

† The values were calculated in accordance with method 2 in cases 1 and 2, with method 1A in cases 3 to 8, with method 1B in cases 9 to 11 and with method 1 in cases 12 to 19.

this particular case injection of 0.04 mg. caused tetanus which killed 4 white mice and 8 guinea pigs, although one-tenth this amount, 0.004 mg., failed to kill 2 white mice.

If the results of the titrations, presented in table 7 and figure 2, are to be put to practical use in the serotherapy of human tetanus, it becomes necessary to calculate the lethal dose of toxin for man with reference to the material employed in this study. If 0.01 mg. is arbitrarily accepted as a certainly fatal dose for a guinea pig weighing 250 Gm., it probably would require about 3 mg. to cause fatal tetanus in a person weighing

TABLE 8.—*Results of Injection of Toxin into Control Animals*

Dose of Toxin		Weight of Test Animal, Gm.†	Days After Injection of Toxin						
Mg.	Percentage of L+ Dose *		1	2	3	4	5	6	7
0.095-0.100	14-15	420-530	D (2)‡	D (1)	....	....	....	....	....
0.057-0.072	8-10	450-480	....	DD (1)	....	....	....	....	....
0.040-0.050	6-7	15-25	DDDD (12-19)	....	....	....	....	....	....
		200-300	....	DDD (3-8) D (2) D (9-11)	D (9-11) D (8)				
		500-580	....	DD (1)	....	....	....	....	....
0.020	3	380	....	....	....	D (2)	....	....	....
0.010	1.5	15-25	....	D (12-18)	....	....	....	....	....
		235-300	D (2)	....	D (4-7)	....	....	....	....
0.004	0.6	15	....	....	....	....	....	....	RR (19)
0.0024	0.3	230-240	....	DD (2)	....	....	....	....	....
0.0010	0.1	15-25	....	....	....	....	DD (12-18)	....	....

* The L+ (test) dose equals approximately 100 minimal lethal doses (for a 350 Gm. guinea pig).

† Animals weighing 15 to 25 Gm. were white mice, and those weighing 200 Gm. or more were guinea pigs. If it is assumed that the average susceptibility of the guinea pig to tetanus toxin is about thirteen times that of the white mouse, a white mouse weighing 15 Gm. corresponds to a guinea pig weighing about 200 Gm.[3]

‡ The numbers in parentheses indicate the case numbers recorded in table 7. D signifies death and R recovery.

approximately 150 pounds (68 Kg.) and correspondingly less for children.[32]

The titers given in table 7 are shown in graphic form in figure 2. This chart shows that of the 21 specimens of human blood serum collected from the 14 patients with tetanus, six to forty-two days after the injection of 20,000 to 100,000 units of tetanus antitoxin, 15 (cases 2, 6 to 11 and 15 to 19) neutralized over 1 mg. of toxin, 5 (cases 3, 4, 5, 7 and 8) 0.1 to 1 mg. and only 1 (case 15) 0.01 to 0.1 mg. In this last instance, however, the relatively low titer was determined on a specimen of blood obtained thirty-five days after the injection of 60,000 units of antitoxin,

32. This calculation is based on acceptance of the statement[4a] that man is about 85 per cent as susceptible to tetanus toxin as is the guinea pig.

whereas a high titer was detected in a sample of serum obtained on the twenty-first day after serum treatment, or two days after the patient had been discharged as cured.

In 4 instances (cases 2, 7, 8 and 15) titrations were carried out on serial specimens of human blood serum secured from six to forty-two days after the injection of therapeutic doses of antitoxin. In every instance the general trend was toward a decrease in titer with the passage of time. Significant amounts of antitoxin persisted in the blood of all 4 patients up to the time of discharge from the hospital. The results for the patient in case 7 are of particular interest. This patient had been hospitalized for forty-three days because of persistent generalized spas-

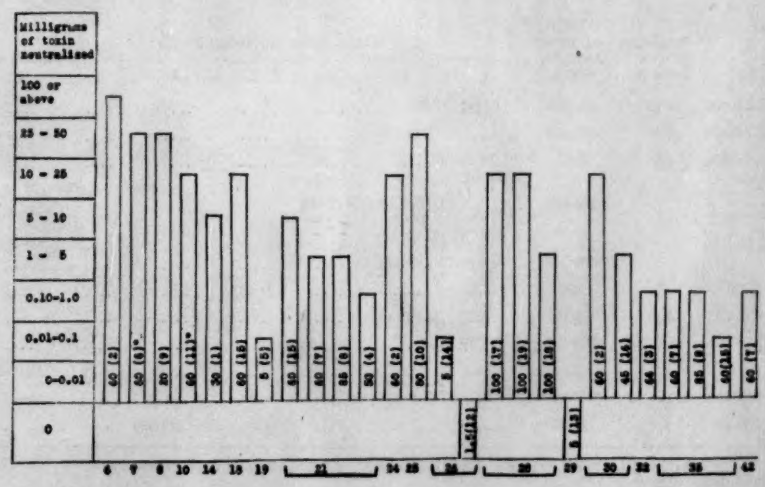

Fig. 2.—Antitoxin titers for 14 patients with tetanus and for 5 other patients, all of whom were given tetanus antitoxin. All titers are expressed in milligrams of toxin neutralized by 1 cc. of blood serum. The numbers preceding parentheses give the dose of antitoxin in thousands of units; those enclosed in parentheses indicate the case number, as given in table 7. An asterisk indicates that the patient died.

ticity. A specimen of blood taken one day before discharge from the hospital contained a significant amount of antitoxin, for 1 cc. of the serum neutralized 0.1 to 1.0 mg. of toxin. In case 15, however, 1 cc. of blood serum obtained thirty-five days after the injection of therapeutic serum (sixteen days after discharge from the hospital) neutralized only 0.01 to 0.1 mg. of toxin. It is to be restated, however, that in this case the titer was high twenty-one days after the termination of antitoxin treatment (two days after the patient was sent home from the hospital), at which time 1 cc. of the blood serum neutralized 5 to 10 mg. of toxin.

Specimens of blood obtained by cardiac puncture immediately after death in cases 6 and 11, on the seventh and the eleventh day, respectively,

after the intravenous injection of 60,000 units of antitoxin, neutralized large amounts of tetanus toxin. In both cases clinical evidences of bronchopneumonia were noted during life and they were confirmed by necropsy in case 6.[33]

For truly comparative study titers are best expressed in terms of units of antitoxin per cubic centimeters of blood serum. However, under the conditions of these experiments certain observations are worthy of mention. Of 4 specimens of blood obtained twenty-one days after the injection of antitoxin, that secured from a patient who had received 85,000 units (case 8) showed no higher titer than did the samples taken from 2 other patients (cases 7 and 15) who had been given 60,000 units. Similarly, examination of the 3 samples of blood drawn thirty-five days after the administration of 60,000 to 85,000 units of antitoxin showed no consistent relation between the amount of therapeutic serum employed and the neutralizing power of the blood serum. These varying results cannot be consistently explained on the basis of differences in body weight, and therefore of blood volume, among the various patients. These observations are of particular interest because they raise the question pertaining to a possible relation between the dose of antitoxin injected and the level and duration of the passive immunity conferred thereby. On this question, however, there are conflicting points of view. In applying the formula of Thorvald Madsen [34] to the data collected in a study of the blood titer curves of patients with a diphtheria given specific serum, Erin Madsen [29b] found that the curves were not significantly different when they were corrected for body weight (and therefore for blood volume) of the patients, for the doses of antitoxin administered and for the unavoidable inaccuracies encountered in the use of therapeutic serum. However, a review of Madsen's data [35] suggests that there may be a direct relation between the dose of antitoxin injected and the total amount of circulating antibody present weeks (four in this particular study) after the administration of specific serum. Likewise, Bulloch [36] decided on the basis of an experimental study of the duration of passive diphtheria immunity that the period over which passive immunity persisted was probably influenced by the amount of antitoxin originally introduced into the body. In reference to other antibodies,

33. The necropsy was inadequate in case 9; so a final statement concerning the condition of the lungs is precluded.

34. Madsen, T.: The Decrease of Antibodies in the Organism Indicated by a Formula, in Festskrift ved indvielsen af Statens Serum Institute, Copenhagen, O. C. Olsen & Co., 1902, no. 8.

35. Madsen,[29b] p. 113.

36. Bulloch, W.: The Durability of Passive Diphtheria Immunity, J. Path. & Bact. **5**:274-278, 1898.

Bulloch [36] quoted Ehrlich [37] as saying that "the antiricin body was present for a relatively long period in the circulation . . . and depended on the amount of antiricin introduced." On the other hand, Ramon, Debré and Bernard [29a] have called attention to the fact that, other conditions being equal, marked variations may be noted in the titers of different serum-treated patients. They emphasized that this phenomenon was related more directly to the reaction of the patient (active immunity?) than to the dose of antitoxin employed or to the severity of the toxemia. In similar fashion, Sohier and Jude,[28] correlating their own observations on the blood titer curve of a patient with tetanus who was given repeated doses of specific serum (total, 1,254,000 international units) with the results of other studies [29a] on diphtheria, pointed out that the blood titer attains a certain level and is not significantly influenced by further serotherapy. The observations of Thorvald Madsen,[34] Sohier and Jude [28] and Bulloch [36] indicate that the disappearance of the antitoxin (of tetanus or diphtheria) from the blood is dependent on a metabolic process rather than on excretion by the kidneys.

As was noted in figure 2 and table 7, 4 of the titrations were carried out on specimens of blood serum secured from 4 patients who had received prophylactic doses of antitoxin varying from 1,500 (case 12) to 5,000 (cases 5, 13 and 14) units. At the end of twenty-six days the patient who had received 1,500 units had no demonstrable antitoxin, whereas one (case 14) given 5,000 units showed a low, but appreciable, antitoxin titer. At the end of nineteen days the patient in case 5, who had received 5,000 units of antitoxin, had a relatively low titer, whereas the one in case 13, who had been given a similar prophylactic dose, had no demonstrable antibody at the end of twenty-nine days. The limited period of protection conferred by these relatively low doses of antitetanus serum has been pointed out before.[38] Comparison of the titers in cases 5 and 15 is of interest because the intervals between the injection of antitoxin and the collection of blood specimens were approximately the same (nineteen days for case 5 and eighteen days for case 15), whereas the doses differed (5,000 units for prophylaxis in case 5 and 60,000 units for treatment in case 15). A higher titer was noted in the blood serum in case 15, in contrast with a relatively low titer in case 5. Similarly the high titers in cases 2 and 10, on the twenty-fourth to the twenty-fifth day after the injection of 60,000 to 80,000 units of antitoxin, are in marked contrast with the low titers in cases 12 and 14 on the twenty-sixth day after the administration of prophylactic doses of 1,500 and

37. Reference to the publication of Ehrlich, from which Bulloch quoted, could not be located in the literature.

38. Sacquepee, E., and Jude, A.: Sur l'immunité conférée par le sérum antitétanique, Rev. d'immunol. **3**:444-448, 1937. Spaeth.[1] Bigler, J. A., and Werner, M.: Active Immunization Against Tetanus and Diphtheria in Infants and Children, J. A. M. A. **116**:2355-2366 (May 24) 1941.

5,000 units, respectively. The absence of antitoxin in case 13 on the twenty-ninth day after the injection of a prophylactic dose of 5,000 units contrasts sharply with the presence of high titers in the specimens of blood obtained in cases 17, 18 and 19 on the twenty-eighth day after the administration of 100,000 units of antitetanus serum. The presence of a high titer in case 1 on the fourteenth day after the intravenous injection of 30,000 units of tetanus antitoxin for nonspecific treatment compares favorably with the titer observed in case 15 on the eighteenth day after the administration by vein of 60,000 units for active therapy.[39]

In reviewing the titration data presented in this study, the question has constantly arisen concerning the relative roles of active and passive immunity in establishing the persistent antitoxin levels in the blood of the patients treated with specific serum. The settlement of this problem, contrary to the opinion of Dean,[26] is a matter of more than academic interest. If passive immunity played a predominant or sole part in maintaining adequate levels of neutralizing antibody, a more certain protection could be anticipated than would be expected if the more variable factor of active immunity were involved. If active immunity were the important basic factor, the possible need of inducing this form of protection by means of tetanus toxoid as a follow-up procedure after the administration of antitoxin would have to be seriously considered. In fact, such a technic of treatment [40] has been recommended by others as a routine in the management of patients who have either tetanus or diphtheria. Obviously, from the data presented in this paper one is not justified in making any final statement concerning the parts played by passive and active immunity. An adequate number of controls has not been available because of the low doses of antitoxin currently employed for the prophylaxis of tetanus. Nevertheless, it is worthy of restatement that in case 1 the patient, who did not have tetanus, had a high titer fourteen days after the intravenous injection of 30,000 units of antitoxin. Likewise, the remarkable consistency with which therapeutic doses of antitoxin were associated with high titers and prophylactic amounts with low titers suggests that the amounts of antitoxin injected, up to a certain dose, may definitely influence both the level and the duration of the passive immunity conferred. In this respect it is of interest that Sohier and Jude [28] have expressed the opinion that the antibodies detected at various intervals after serotherapy represent those originally injected

39. According to the studies of Sohier and Jude [28] and Madsen,[34] relatively minor changes in the titers occur from the fourteenth to the eighteenth day after the injection of antitoxin. Consequently, the titers in cases 1 and 15 may be compared despite the difference in the time at which blood specimens were secured for titration.

40. Ramon, G.: Combined (Passive-Active) Prophylaxis and Treatment of Diphtheria or Tetanus, J. A. M. A. **114**:2366-2368 (June 15) 1940.

because tetanus is not an immunizing disease. Likewise, it is pertinent and interesting to point out that Yasayuma and Schobl [6] demonstrated toxin, rather than antitoxin, in the blood of a patient who had tetanus of approximately two months' duration. Obviously, a final answer to this problem can be reached only by a study of the passive immunity curves of normal persons given injections of various amounts of tetanus antitoxin and by subjecting the data thus obtained to analysis in terms of the formula propounded in 1902 by Thorvald Madsen.[34] Because of its practical importance, both for serotherapy and for seroprophylaxis, such a study is definitely indicated.

It is of interest that of the 21 specimens of serum collected from six to forty-two days after the injection of 45,000 to 100,000 units of antitetanus serum, 3 were obtained from patients with mild symptoms of tetanus, 1 from a patient with a moderately severe form of the disease and the rest from those with a severe form. Because of the limited number of patients in each category, one is not justified in drawing any conclusions concerning the relation between the severity of the tetanus and the rate of disappearance of antitoxin from the blood. It is of interest, however, that Ramon, Debré and Bernard,[29a] in their studies of antitoxin curves of serum-treated patients with diphtheria, found no relation between the severity of the disease and the level of antitoxin in the circulating blood.

COMMENT

The available evidence indicates that tetanus toxin gains access to the general circulation after being elaborated at the focus of infection. The logical treatment, therefore, seems to be the maintenance of a liberal excess of antitoxin in the circulating blood until the patient has recovered completely from the attack of tetanus. At least 90 per cent of all fatalities occur during the first ten days of the disease, with some deaths occurring later from complications (particularly pneumonia) or from conditions not essentially related to tetanus.[1] According to my experience, patients treated with antitoxin who survive the first week of hospitalization are usually well on the road to recovery ten days or less after the injection of specific serum. In the event of persistent generalized spasticity (case 7) or a late recurrence of convulsions (case 2), the treatment indicated is the continuation or the resumption of sedative therapy and not the injection of additional antitetanus serum. For these reasons it might be restated that a high titer of antitoxin seems necessary during the first two weeks of the disease and a much lower one from then to the time of discharge from the hospital.[1] The maximum period of hospitalization of the patients for whom data are recorded in table 7 and of those observed elsewhere [41] has been forty-three days.

41. Spaeth, R.: Unpublished data. Spaeth.[1]

Table 7 and figure 2 show that single intravenous or intramuscular doses of 20,000 to 100,000 units of tetanus antitoxin are associated with the presence, over a period of at least six to forty-two days, of amounts of circulating antitoxin theoretically adequate to neutralize quantities of toxin probably lethal for man. However, it is difficult to select the optimal dose of antitoxin on the basis of the data presented in this paper. Nevertheless, it is significant that the titer of the patient in case 1, a control subject, was high on the fourteenth day after the administration of specific antitetanus serum. Likewise, it is noteworthy that the level of antitoxin in the blood serum in case 16 was high thirty days after the intramuscular injection of 45,000 units of specific serum. These

TABLE 9.—*Relation Between Dose of Antitoxin and Clinical Outcome in 92 Cases of Tetanus* *

Dose of Antitoxin, 1,000 Units	Mild and Moderate Forms of Tetanus		Severe Form of Tetanus		Total		
	Recovery	Death	Recovery	Death	Recovery	Death	R/D †
100	9 (1)‡	1	2	6 (4)§	11	7	1.5
81-90	1	..	..	..	1	..	...
71-80	9 (1)	..	6 (2)	5 (4)‖	15	5	3.0
61-70	2	..	1	..	3	..	...
51-60	9	..	2	12 (7)	11	12	0.9
41-50	3	1 (1)	..	1 (1)	3	2	1.5
31-40	11	..	..	7 (4)	11	7	1.5
21-30	2	..	..	..	2	..	...
20	2	..	..	..	2	..	...

* All serum was given by muscle or by vein during the first twenty-four hours of hospitalization except in the cases of 2 patients who received the total amount over a period of two to three days (in Cook County Hospital, Chicago, between July 1933 and July 1940). Only 1 death occurred among the 17 patients first given serum after the fourth day of the disease.

† R/D is the ratio between recoveries and deaths.

‡ The figures in parentheses indicate the number of cases in which the patient had pneumonia.

§ Includes the cases of a 60 year old man with a markedly irregular heart beat (he required digitalis) and a 19 year old woman with pneumonia and septic parotitis.

‖ Includes the cases of a 6 year old boy with septic parotitis and pneumonia and a 59 year old man with pneumonia, marked stomatitis and evidences of marked deprivation and neglect.

observations are of particular importance because the study of Dean [26] (table 4) showed that single intravenous doses of 30,000 units of antitetanus serum were followed by significant antitoxin titers in specimens of blood drawn six to thirty-nine days later. Dean [26] stated that in his experience no improvement in clinical results was observed when the initial intravenous dose of 30,000 units was supplemented by additional doses of serum.

As was noted in a previous report,[1] neither the clinical outcome nor the appearance of the patient gives any clue to the level of antitoxin in the circulating blood, and, furthermore, reliance cannot be placed on conventional statistical methods for determining the optimal dose of antitoxin.[1] For example, table 9 shows that there is no consistent relation between the dose of antitoxin and the mortality rate. This table indicates that both the severity of the disease and the presence of

potentially fatal complications are of cardinal significance in determining the clinical outcome. Since sedative therapy and general nursing and other care are of great importance in facilitating recovery from tetanus, it is of significance that all of the patients for whom data are recorded in table 9 had been given the benefit of such special care. Because of the many extrinsic variables which may influence the clinical results, it obviously becomes necessary to adopt an immunologic, rather than a clinical, approach to determine the proper dose of antitetanus serum. Such a method has been attempted in this study, and the results may be profitably compared with the data obtained by clinical methods. Therefore, table 10 is of interest because it shows the absence of a truly significant difference in the average doses of antitoxin administered during the first twenty-four and the first forty-eight hours of the disease [42] to the patients who recovered and to those who died. The

TABLE 10.—*Average Doses of Antitoxin Used in 169 Cases of Tetanus* *

	First 24 Hr.				First 48 Hr.				Entire Stay in Hospital †			
	Recovery		Death		Recovery		Death		Recovery		Death	
Form of Tetanus	No.	Dose	No.	Dose	No.	Dose	No.	Dose	No.	Dose	No.	Dose
Mild	32	37.7	..	....	32	48.2	..	....	32	91.0	..	....
Moderate	26	35.2	8	41.4	23	56.1	6	73.5	26	119.4	8	103.9
Severe	5	31.2	98	37.0	5	43.2	36	66.2	5	78.2	98	55.4
Total	63	35.8	106	37.4	60	50.8	42	56.8	63	101.7	106	58.1

* The patients were all treated at Cook County Hospital, Chicago (1921-July 1933). The serum was injected by a variety of routes (muscle, vein, spinal canal and cistern). All doses are expressed in thousands of units.

† The average duration of serum treatment for the patients who recovered was 5.3 days and for those who died 1.8 days. The average duration of life after hospitalization among the patients who died was 2.1 days.

data in table 10 suggest that from the clinical standpoint a dose of approximately 35,000 units, or at the most 50,000 units, should be satisfactory for the active treatment of tetanus.

Figure 3, which is reproduced from a previous study,[1] indicates that doses of 20,000 to 30,000 units have proved satisfactory for the treatment of patients hospitalized during the first three days of the disease and amounts as low as 10,000 units have been adequate for patients who were treated on the sixth day of the disease or later.

The observations illustrated in figure 3 are, in general, confirmed by a more detailed analysis of the data which have been condensed to

42. Restriction of the analysis of serum dosage to the amounts injected during the first twenty-four to forty-eight hours of hospitalization is justified on the basis of the studies of Sohier and Jude;[28] Huntington, Thompson and Gordon (The Treatment of Tetanus with Antitoxin: An Analysis of the Outcome in Six Hundred and Forty-Two Cases, Ann. Surg. **105**:93-96 [Jan.] 1937) and Irons (The Treatment of Tetanus by Antitetanic Serum, J. Infect. Dis. **15**:367-377 [Sept.] 1914).

make table 9. Thirty-two deaths occurred among the 75 patients given antitoxin during the first four days of the disease, whereas a single fatality occurred among the 17 given antitoxin later. Of the group treated with serum after the fourth day of the disease, 3 patients received 20,000 to 30,000 units, 7 received 31,000 to 50,000, 3 received 51,000 to 60,000 (1, with a severe form of the disease, died) and 4 received 61,000 to 80,000. Two other patients (both had a mild form of tetanus and data for them are not included in table 9) recovered without the administration of antitoxin. Among those given specific serotherapy during the first four days of the disease there was no consistent relation between the dose of antitoxin and the mortality rate.

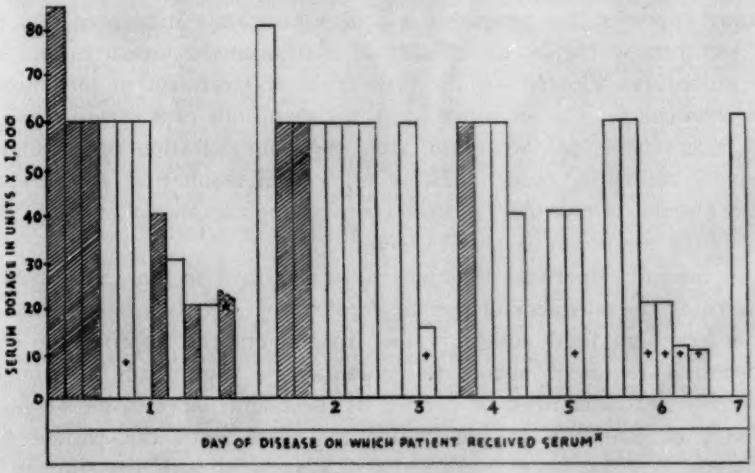

Fig. 3.—Relation between the dose of antitoxin and the clinical outcome in 33 cases of tetanus. The asterisk indicates that the dosage was not recorded. The point marked *X* indicates the day on which the patient was admitted to the hospital. The plus sign indicates mild tetanus. In all other cases the condition was moderate or severe. The shaded columns represent deaths.

Although a dose of 30,000 units probably represents an adequate amount of antitoxin for general use, to avoid underdosage it appears desirable to adhere to the schedule recommended on a previous occasion,[1] namely, 60,000 units for patients admitted to the hospital for serotherapy during the first five days of the disease and 40,000 units for the mildly to moderately ill patients first treated later in the course of the disease.

A proper evaluation of the serum therapy of tetanus necessitates a comment concerning the fundamental action of the specific antitoxin. Tetanus antitoxin apparently exerts no immediately curative action. Symptoms of the disease present at the time of its administration continue unaltered until lysis begins, except as they are temporarily influenced by sedative drugs or exaggerated by an advance in the disease process.

From the clinical standpoint, antitoxin may be considered of value when it prevents a significant advance in the disease process. On certain occasions, as in cases 9 and 11 (table 7), a moderate advance may occur as a result of a natural "forward inertia," despite the administration of doses of antitoxin which induce high blood titers of specific antibody. Frequently the administration of antitetanus serum to patients with overwhelming toxemia or to those first treated late in the disease fails to prevent an advance. Obviously, on such occasions antitoxin has not been clinically effective. It is to be emphasized, however, that a halt in the advance of the disease process does not necessarily lead to recovery. The clinical outcome depends on the phase of the disease in which serum treatment has proved to be effective. If severe asphyxial spasms have already appeared, the prognosis will be significantly influenced, not by the serotherapy but by the efficacy of antispasmodic measures and by the procedures adopted for the prevention or treatment of pneumonia and exhaustion. On the other hand, if convulsions of a severe type do not supervene either before or after the administration of antitoxin, recovery ordinarily occurs. However, a fatal result may ensue, even in the absence of convulsions, from complicating pneumonia or from conditions not essentially related to tetanus.[1]

In the individual case titrations seem to afford accurate information concerning the adequacy of specific serotherapy. As has been indicated by others,[43] an immunologic, rather than a clinical, approach to this problem is required. From the immunologic standpoint, the aim of antitoxin treatment must be defined as the maintenance of an adequate amount of antitoxin in the circulating blood until the patient has recovered.[44] The blood titers must be correlated with the severity of the disease, the associated complications, the duration of the signs and symptoms at the time treatment is first instituted, the kind and degree of sedative and supportive therapy and all other conditions of apparent significance in the ultimate prognosis.[1] Titers can then be correlated with the dosage of antitoxin, on the one hand, and the clinical outcome, on the other.

Titrations are of definite value in determining the relative effectiveness of specific and of nonspecific therapy in the management of patients with tetanus. The study of this problem has been indicated in order that tetanus may be treated on a more scientific basis, that the expense entailed in the use of large doses of antitoxin may be reduced, that patients may be spared both the discomfort and the danger of repeated injections of serum and that the severity both of immediate and of delayed serum reactions may possibly be lessened. A final decision in respect to the

43. Dean.[26] Sohier and Jude.[28]

44. Spaeth.[1] Footnote 43.

details of serotherapy has appeared necessary in order to permit the application of further efforts, both clinical and experimental, to the elaboration of improved methods for the treatment of convulsions and complications. The rapid increase in the literature on the nonspecific therapy of tetanus justifies this point of view.

SUMMARY AND CONCLUSIONS

Evidence, both direct and indirect, has been presented in support of the theory that tetanus toxin circulates in the blood stream before its final fixation in the tissues of the central nervous system occurs. On the basis of the data presented, the intravenous and the intramuscular routes have been considered the channels of choice for the administration of tetanus antitoxin.

The aim of the specific serotherapy of tetanus has been defined as the provision of an adequate titer of antitoxin in the circulating blood during the first two weeks of the disease and a significantly lower titer from that time until discharge from the hospital. The results of the titrations of 21 specimens of human blood serum secured from 14 patients with tetanus six to forty-two days after the intravenous or intramuscular injection of 20,000 to 100,000 units of antitoxin, correlated with the results of titration studies of other investigators and with clinical data obtained from two different institutions, suggest that single doses of approximately 30,000, and probably not more than 50,000, units should be adequate for routine use. The feasibility of employing lower doses for patients first treated after the fourth day of the disease has been discussed. However, in agreement with the principle propounded in a previous report, a routine dose of 60,000 units is proposed for the treatment of patients admitted to the hospital during the first five days of the disease and a dose of 40,000 units for the mildly to moderately ill patients first treated later. It is conceded that such a schedule is necessarily somewhat arbitrary.

The data collected in the titrations of specimens of blood serum obtained from 5 control subjects given injections of 30,000 units (1 patient), 5,000 units (3 patients) and 1,500 units (1 patient) of tetanus antitoxin have been compared with the results of similar studies on samples of blood serum secured from patients with tetanus who were treated with 20,000 to 100,000 units of antitoxin. On the basis of this comparison, the question has been raised concerning the possible relation between the size of the dose of antitoxin administered and the degree and the duration of the immunity thus conferred. The need for further investigations on this phase of the subject has been indicated.

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DISCUSSION

MR. ROBERT R. WILLIAMSON, Chicago: I have examined the data of Erin Madsen on diphtheria antitoxin titers and find that his empiric equation holds. Examination of this equation and a rederivation of it on a kinetic basis indicate that the initial dose of antitoxin must affect both the level and the duration of immunity.

DR. JOSEPH K. CALVIN, Chicago: Dr. Spaeth's fine work is fundamental research of great practical importance in determining and standardizing the dose of tetanus antitoxin. In reviewing clinical cases of tetanus, it is impossible to reach any conclusions as to the proper dose of the antitoxin because of the many variables present in each case, such as the length of the incubation period, the presence or absence of convulsions, the amount of sedation and the day of the disease, to mention only a few. The antitoxin and the sedatives are complementary; that is, the antitoxin prevents further damage to the nervous system from the toxin but does not alter the symptoms already present, while the sedatives control the symptoms (spasms) resulting from the damage already done to the nervous system by the toxin.

From this discussion it can be concluded that the only accurate method of determining the ideal dose of antitoxin is by biologic and immunologic titrations, rather than by clinical observations. Dr. Spaeth has performed a most careful study of this sort, and I believe the dosage he mentioned should be accepted, namely, 30,000 to 60,000 units given intravenously in a single dose, rather than the haphazard administration of doses ranging from 10,000 to 3,000,000 units, which have been reported in the literature as effecting clinical cures. There is also a definite biologic reason for not repeating the dose: The antitoxic titer remains sufficiently high for at least a month to prevent any further damage from the toxin.

DR. ARCHIBALD L. HOYNE, Chicago: Dr. Spaeth has brought out a number of excellent points. In the first place, I think the fact that the tetanus toxin circulates in the blood is frequently neglected. The presence of the toxin in the blood should be sufficient reason for believing that the intravenous method of treatment is proper and that patients with tetanus do not require intraspinal injection of antiserum. Nevertheless, I believe that the usual treament outside Chicago does include intrathecal therapy. Dr. Spaeth apparently regards the serum treatment of tetanus in somewhat the same light as the serum treatment of diphtheria. For many years physicians have aimed at estimating the total amount of diphtheria antitoxin needed and administering the entire quantity at one time.

Why should a patient with tetanus in the late stage receive a smaller dose of antiserum than a patient whose disease is in the early stage, especially if it is thought that tetanus is a nonimmunizing disease? I should also like to ask whether an effort has ever been made to determine the antitoxin titer for a patient with tetanus before he has received any serum. The dose of antitetanus serum I have used has usually been 20,000 units if administered intramuscularly and 40,000 units if given intravenously. I suspect that those who condemn the intravenous method of treatment do not always avail themselves of the best procedures. If correct safeguards are applied, I think there are not likely to be any extremely severe reactions.

DR. S. J. HOFFMAN, Chicago: I cannot help but feel that the prophylactic treatment of tetanus should be discussed. To me the indications for such treatment have always been an enigma. I remember the case of a nurse who was injured in an automobile accident; a surgeon insisted that no antitoxin be used, and the nurse died.

Pediatricians encounter many minor injuries, for children are always falling and hurting themselves, but the question of prophylactic treatment has never been taken up. Does Dr. Spaeth have any ideas?

DR. RALPH SPAETH, Chicago: With reference to the high doses cited by Dr. Calvin, I might state that amounts as high as 3,000,000 units have been given. Sohier and Jude reported the case of a patient who received 1,254,000 international units. The blood titers were determined over a period of at least three months and were found to be high. They pointed out that it was impossible to raise the titer beyond a certain level despite the repeated injection of large doses of serum. I should ascribe that phenomenon to a metabolic response on the part of the body to foreign protein. Cables reported the case of a patient who was given more than 1,000,000 units of tetanus antitoxin, and the fact that recovery occurred led him to recommend the administration of antitoxin until remission of the disease takes place. I think the data presented this evening would contradict that point of view.

Dr. Hoyne mentioned intraspinal serotherapy. That method must be condemned, for various reasons. First, direct and indirect evidence clearly shows that tetanus toxin reaches the central nervous system by way of the blood stream, not by spreading along the nerve trunks. Second, serum introduced into the cerebrospinal fluid rapidly finds its way into the blood stream. Third, intraspinal serotherapy is dangerous. I have seen 1 patient in whom the only sign of tetanus was trismus in the presence of a local lesion on the leg, which was believed to be the focus of infection. Within one hour after intraspinal serotherapy was instituted this patient had severe convulsions, which defied intensive sedative treatment. At necropsy serum meningitis and moderate amounts of free blood over various portions of the cerebrum and the cerebellum were observed. In reviewing the records of cases of tetanus in Cook County Hospital (1921 to 1933), I found at least 10 instances in which death occurred almost immediately or shortly after intrathecal administration of antitoxin. Some patients had survived for four to nine days without treatment, only to die rapidly after the intraspinal injection of the specific serum.

The theory has been prevalent that serum injected into the veins is lost much more rapidly than that introduced by the intramuscular or subcutaneous route. Thorvald Madsen, in 1902, pointed out that excretion by the kidneys plays a negligible role in the disappearance of antibodies from the human body. A metabolic process is apparently responsible. Therefore, after the peak of the titer has been reached, the rate of disappearance of antibodies from the body is independent of the route of injection.

Dr. Hoyne suggested that the serum treatment of diphtheria is similar to that of tetanus. Erin Madsen has shown in his serum treatment of diphtheria that twenty-eight or more days after the injection of 45,000 to 60,000 units of specific serum into the muscle or the vein the titer is high; in other words, this low single dose is satisfactory for treatment. I might point out that tetanus antitoxin is ten times as potent as diphtheria antitoxin; 1 unit of the former neutralizes about 1,000 minimum lethal doses of specific toxin, whereas 1 unit of the latter neutralizes only 100 minimum lethal doses.

In reply to Dr. Hoyne's question as to why less serum should be given to patients with the late stage of the disease, I should say that tetanus differs from diphtheria in that the patients who seek hospitalization late in the course of tetanus have a mild form of the disease, whereas a large percentage of the patients seen late in the course of diphtheria have a clinically malignant form of

the disease. Obviously, the occasional patient with a severe form of tetanus who is first treated after the fourth or fifth day of the disease ought to receive the higher doses of serum recommended.

I cannot give extensive figures from the literature on the titer prior to administration of antitoxin. I have a patient who was admitted near the end of the second week of the disease. I plan to determine her blood titer before the serum is injected. Sohier and Jude, on the basis of their review of the literature, stated that tetanus is not an immunizing disease.

Reactions from the intravenous administration of serum have been relatively infrequent and are of minor significance if the serum is given slowly (60 drops a minute) after being diluted with 500 to 1,000 cc. of physiologic solution of sodium chloride or some other customary vehicle.

Dr. Hoffman brought up the question of indications for the use of antitetanus serum. I have no basis on which to make a decision. The tetanus bacillus is represented by many strains, some of which produce large amounts of toxin, while others liberate negligible amounts or none. For this reason, many marked local lesions do not cause tetanus, whereas trivial lesions may be followed by a fatal form of the disease. Frequently one can find no evidence of a local lesion, although it always must be present somewhere on the body.

I think the whole population should be actively immunized against tetanus by means of tetanus toxoid. A stimulating dose of toxoid should be given in the event of a later injury. A problem arises when a child is brought to the physician with an injury but without previous active immunization. In such circumstances the wisest course is to give 5,000 units of antitetanus serum, or, if an interval of several days has elapsed since injury, 10,000 or even 20,000 units. In other words, as the interval between injury and treatment becomes appreciable, the dose of serum should be increased. I wish to emphasize that 1,500 units is not adequate for prophylaxis. In too many cases tetanus has followed the injection of this small dose. Ramon and his associates have advised the simultaneous injection of antitoxin and of toxoid in those patients who have not been actively immunized. The active immunization program is completed in the customary manner. I have found that two injections may cause too much discomfort and the patient may not return for subsequent inoculations. I prefer giving the antitoxin alone and having the patient come back several weeks later to begin the series of injections of toxoid.

COURSE AND PROGNOSIS OF HEMORRHAGIC NEPHRITIS IN CHILDREN

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In this article are reported observations on the course and prognosis in 188 cases of hemorrhagic nephritis in persons below the age of 15 years who were observed at the Strong Memorial and Rochester Municipal Hospitals between June 1926 and October 1939. Since one of these hospitals has facilities for the care of contagious diseases, the cases of nephritis developing as complications of such diseases are included in this study.

The diagnosis of nephritis in these cases was based on the occurrence of albumin, blood and casts in the urine, with variable degrees of edema, hypertension, anemia and nitrogen retention. There was nearly always a history of a recent preceding infection, usually of the respiratory tract. Only 3 cases are included in which the diagnosis was based on what might be called "minimal evidence." In all 3 there were albuminuria after an acute infection and on two or more occasions an abnormal number of red blood cells in the urine, determined by the technic of Addis.[1] In 1 case the patient had hypertensive cardiac failure early in the course of her nephritis but did not show an abnormal number of red blood cells in the urine until a month after onset.

The cases here reported have been studied by observing the changes in renal function, at short intervals during the acute stage, by trying to correlate the rate of change of renal function during the acute stage with the ultimate outcome of the nephritis and by determining later, when possible, the completeness of recovery from the disease.

METHODS

The well known urea clearance test of Möller, McIntosh and Van Slyke,[2] as adapted for use with children by McIntosh, Möller and Van Slyke,[3] has been used

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1. Addis, T.: A Clinical Classification of Bright's Disease, J. A. M. A. **85**: 163 (July 18) 1925.

2. Möller, E.; McIntosh, J. F., and Van Slyke, D. D.: Studies of Urea Excretion: II. Relationship Between Urine Volume and the Rate of Urea Excretion by Normal Adults, J. Clin. Investigation **6**:427, 1928.

(Footnotes continued on next page)

since 1931 to determine the level of renal function. The test was nearly always done in the morning after breakfast which usually consisted of toast, jam or jelly and water. Milk, coffee, tea and cocoa were not given preceding a test. In certain cases in which the output of urine was low the test was continued for several hours in order to minimize the error in urinary volume resulting from incomplete emptying of the bladder. For the same reason, an effort was always made to produce a good water diuresis. Two specimens of urine were collected for each test, and samples of blood were taken at approximately the middle of each period of urine collection. Patients who were in the hospital were nearly always in bed during the test. Tests performed subsequent to the patient's discharge were done in the outpatient department, with the patient ambulatory. In reporting the results, an average of the clearances for the two periods is given. For a few patients whose clearances for the two periods were in marked disagreement the results are not included. The clearances are reported as percentages

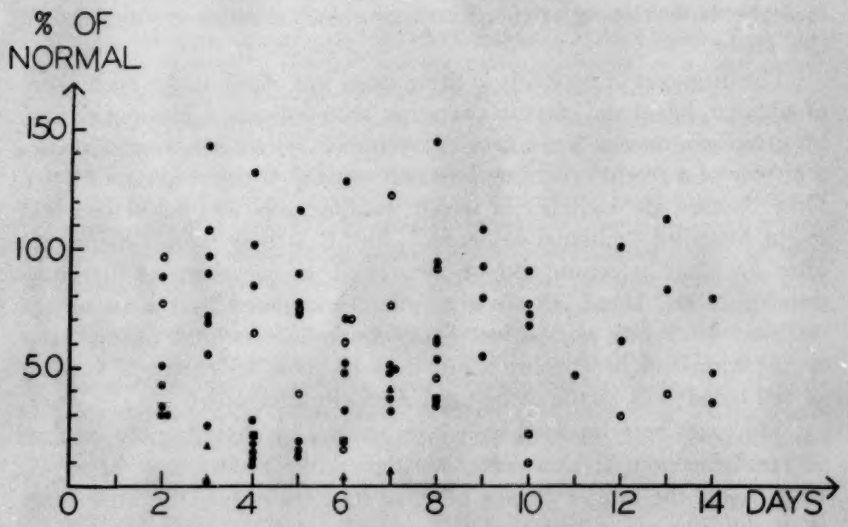

Chart 1.—Initial urea clearance and outcome in 84 cases of nephritis. The triangles indicate cases in which the disease became chronic (5), the solid circles cases in which the patient recovered (55), the hollow circles cases in which the outcome was uncertain (20) and the squares cases in which there was residual albuminuria (4).

of normal. The results of the two types of clearances, "maximum" and "standard," were considered to be comparable, as was found by Cullen, Nelson and Holmes.[4]

3. McIntosh, J. F.; Möller, E., and Van Slyke, D. D.: Studies of Urea Excretion: III. The Influence of Body Size on Urea Output, J. Clin. Investigation **6**:467, 1928.

4. Cullen, G. E.; Nelson, W. E., and Holmes, F. E.: Studies of Kidney Function in Children; Urea Clearance Values: (1) No Evidence of Kidney Disease; (2) After Acute Hematuric Nephritis Following an Acute Infection; (3) In the Acute Stage of Hematuric Nephritis, J. Clin. Investigation **14**:563, 1935.

In this study no support was found for the belief expressed by Holt [5] that the "augmentation limit" is more variable in children than in adults. The only practical application of this question is whether one shall use the formula for the "maximum" or that for the "standard" clearance, with a corrected urinary volume of about 2 cc. per minute. As a result of calculating both types of clearance in 200 tests in which the corrected urinary volume was just below, at or above 2 cc. per minute, I found that for corrected volumes of 1.9 to 2 cc. per minute it makes no practical difference which formula one uses. The mathematical relation between the "standard" and the "maximum" clearance formula is such that they agree for a corrected urinary volume of 1.93 cc. per minute.

The determinations of urea in the blood or urine were made by means of the urease manometric method of Van Slyke, as given by Peters and Van Slyke. In the determinations of blood urea, the test was repeated until satisfactory checks were obtained, usually to 1 mm. on the manometer. In the case of the values for urine, similar checks were obtained, except that in a few instances a difference of 2 mm. was accepted as satisfactory. I made all determinations except during my short absences, when they were done by another person.

An effort was made to do a urea clearance test as early as possible on all children who were admitted to the hospital with nephritis or in whom the disease developed while they were in the hospital during the period from March 1931 to October 1939. Whenever possible, the test was repeated at intervals of about a week during the patient's stay in the hospital if the disease was in an early acute stage and at longer intervals when it was believed that no rapid change in renal function was taking place. Also, an effort has been made to have patients who have had nephritis return from time to time so that the level of urea clearance could be determined and, when possible, the urinary sediment could be examined by the Addis technic.

RESULTS

In chart 1 are shown the initial urea clearances in 85 cases in which tests were done within two weeks of the onset of the nephritis, correlated with the outcome of the nephritis. Only the initial urea clearance is given; results of subsequent tests are not indicated here. It will be seen that patients who showed marked decrease of renal function during the acute stage recovered and that other patients whose nephritis progressed to the chonic stage had higher urea clearances in the acute stage than some patients who recovered. Nevertheless, it is true that in the cases with less favorable outcome the patients were more apt to show lower levels of renal function during the acute stage than did the patients who recovered.

In table 1 are shown the values obtained by serial determinations of the urea clearance during the course of acute nephritis in 60 cases classified according to the outcome of the disease. Data are included for all children for whom three or more satisfactory determinations of urea clearance were obtained during the acute stage of the disease. In 41 of the 60 cases the patient is considered to have recovered, in 10

5. Holt, L. E., Jr.: Urea Clearance Tests: Their Limitations as a Measure of Renal Function in Childhood, Am. J. Dis. Child. **44**:306 (Aug.) 1932.

TABLE 1.—*Urea Clearances* in Sixty Cases of Acute Nephritis*

Patient	Sex	Age, Yr.	Day After Onset									
A. Cases in Which Patient Recovered												
A. C.	M	14	11 79%	15 74%	52 74%	73 99%						
D. G.	M	6	12 61%	26 78%	61 64%	73 67%	120 132%					
L. H.	M	4	7 50%	14 29%	20 23%	29 86%						
A. B.	M	8	3 21%	7 47%	15 51%	21 111%						
L. G.	M	8	6 71%	22 74%	41 106%	83 115%						
A. B.	M	10	4 18%	10 47%	15 40%	28 76%	34 87%	42 87%	48 107%			
A. T.	M	10	10 73%	19 68%	28 77%							
F. V.	M	6	5 78%	14 43%	21 68%	29 70%						
P. A.	M	5	8 61%	15 64%	22 80%	33 119%						
J. T.	M	13	9 88%	16 127%	23 109%							
C. H.	M	12	23 54%	27 49%	34 55%	41 72%	48 60%	58 85%				
F. A.	F	13	8 95%	14 70%	28 114%	44 110%						
J. C.	F	3	7 50%	13 60%	27 74%	34 103%	44 98%	65 141%				
C. S.	F	10	4 14%	9 28%	14 28%	22 64%						
D. W.	F	4	2 43%	9 58%	16 83%	27 69%	29 79%	37 121%				
P. M.	F	6	3 26%	8 50%	12 47%	23 95%						
J. A.	F	11	4 102%	20 118%	41 86%	48 91%	69 126%					
L. M.	F	9	22 60%	28 60%	40 76%	46 91%	53 93%	67 90%	74 104%			
G. S.	M	6	7 32%	11 52%	15 85%							
L. S.	M	9	4 13%	8 50%	14 60%	20 80%						
N. G.	M	5	12 132%	19 134%	26 101%							
M. M.	F	10	5 15%	11 41%	18 81%	23 84%	30 74%	37 108%	47 97%			
M. S.	F	6	14 35%	24 50%	32 68%	38 54%	45 73%	55 94%				
E. P.	M	7	11 47%	25 30%	35 39%	[cardiac failure]						
C. B.	F	7	2 51%	11 52%	17 80%	25 67%	31 102%					
J. E.	F	6	2 34%	5 30%	12 55%	19 56%	26 53%	32 91%				
J. D.	F	2	5 73%	21 68%	30 78%							
C. S.	F	10	9 55%	16 51%	24 65%	31 66%	41 77%					
J. C.	F	13	3 143%	10 72%	13 79%	23 88%	30 109%	37 94%	44 97%	51 114%	70 130%	87 97%
J. H.	F	14	8 54%	16 102%	22 99%							
C. B.	M	12	6 32%	14 72%	23 102%							
T. B.	M	12	3 90%	20 108%	26 71%							
F. C.	M	8	5 97%	15 56%	22 87%	29 55%	42 95%	49 80%	70 100%			

TABLE 1.—*Urea Clearances* in Sixty Cases of Acute Nephritis—Continued*

Patient	Sex	Age, Yr.	Day After Onset										
A. Cases in Which Patient Recovered—Continued													
E. M.	M	5	5 13%	12 64%	19 109%	26 89%							
E. M.	M	10	4 85%	11 83%	22 90%	35 88%							
K. H.	M	13	3 72%	10 55%	17 51%	27 60%	34 88%	41 88%	61 76%				
C. C.	M	12	8 34%	14 43%	21 45%	28 50%	39 56%	52 84%	67 85%	90 109%			
B. T.	F	9	6 48%	20 68%	31 100%								
V. P.	F	10	2 89%	9 112%	25 144%								
H. L.	F	9	4 28%	11 42%	17 57%	24 79%	34 67%	63 99%					
R. R.	F	4	44 47%	57 95%	80 115%								
B. Cases in Which Outcome Was Uncertain													
N. R.	M	6	11 59%	19 77%	31 93%	47 109%							
D. L.	F	10	3 108%	16 76%	21 70%	28 107%							
J. N.	M	5	19 35%	27 78%	64 114%								
R. R.	M	12	12 30%	18 41%	28 61%	42 72%	50 108%						
C. S.	M	2	10 10%	17 53%	24 51%	35 69%							
J. K.	F	10	10 22%	17 28%	24 75%								
R. C.	M	3	13 39%	22 40%	30 32%	37 70%	44 93%						
R. B.	M	2	6 61%	16 64%	47 54%								
M. F.	F	5	3 50%	9 66%	19 92%	29 110%							
M. M.	F	7	6 16%	20 59%	35 76%								
C. Cases in Which There Was Residual Albuminuria													
R. S.	M	4	8 35%	17 146%	26 137%								
G. C.	M	3	4 22%	11 38%	18 75%	26 47%	32 65%	39 71%	48 85%	56 88%	98 103%	119 80%	
R. G.	M	8	6 19%	13 34%	20 45%	38 61%	41 35%	[Infection]		45 60%	52 72%	65 100%	
			79 76%	95 79%	112 90%								
A. S.	F	10	3 2%	5 8%	9 10%	14 43%	23 51%	55 90%					
D. Cases in Which the Nephritis Became Chronic													
F. A.	M	12	7 6%	10 8%	14 22%	20 22%	30 37%	36 43%	43 41%	50 48%	64 58%	73 57%	96 60%
L. S.	M	14	7 41%	13 44%	20 49%	28 46%	34 47%	41 53%	48 54%	55 71%	63 61%	70 80%	77 79%
			84 84%	91 83%	105 97%	119 102%	140 115%	151 109%					
P. M.	M	..	6 4%	11 10%	19 31%	27 36%	38 42%	48 44%	59 60%	123 69%			
M. F.	M	..	8 62%	15 64%	24 71%	38 68%	59 64%	71 74%	87 77%	92 78%	99 81%	122 85%	
J. DeS.	M	..	3 17%	10 12%	12 17%	13 18%	21 28%	27 30%	34 34%	41 48%	49 57%	56 55%	66 73%
			81 83%	99 66%									

* Urea clearance is expressed as per cent of normal.

it has not been possible to determine the outcome of the nephritis, in 4 the child was left with a slight albuminuria which was independent of posture (in the table designated as "residual albuminuria") and in 5 the nephritis progressed to the chronic stage. The basis for assuming recovery and chronicity will be presented later.

Chart 2 shows the averages of the urea clearances in each of these four groups of cases by ten day periods, starting from the onset of the nephritis. If a urea clearance of 80 per cent of normal is taken as indicating the lower limit of normal renal function, it will be observed that the average of the urea clearances in the group of cases in which

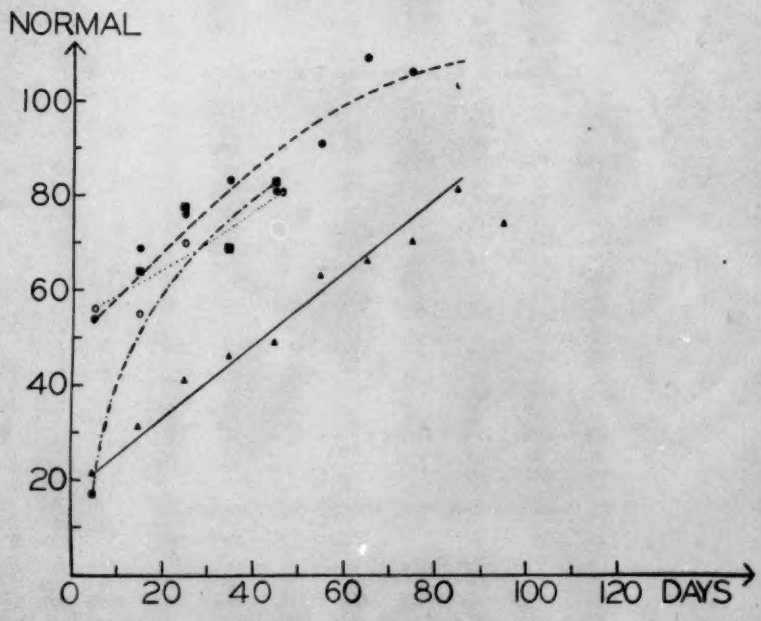

Chart 2.—Average levels of urea clearance in 60 cases of acute nephritis. The triangles indicate cases in which the disease became chronic (5), the solid circles cases in which the patient recovered (41), the hollow circles cases in which the outcome was uncertain (10) and the squares cases in which there was residual albuminuria (4).

the patient recovered reached this level in thirty-three days, the average in the 10 cases of uncertain outcome reached it in forty-five days and the average in the 4 cases in which there was residual albuminuria reached it in forty-one days, while it was eighty-one days before the average of the urea clearances in the 5 cases in which the nephritis progressed to the chronic stage reached this level. At the end of one month after onset of the nephritis, the urea clearance in 16 of the 41 cases in which the patient recovered had not reached 80 per cent of

normal. In 6 of the 10 cases of uncertain outcome, in 3 of the 4 cases in which there was residual albuminuria and in all 5 in which the disease progressed to the chronic stage this level had not been reached in one month. At the end of two months after onset of the nephritis, the urea clearances in all but 2 of the 41 cases in which the patient recovered and in all 4 of the cases in which there was residual albuminuria the level of 80 per cent normal had been reached, while in none of the 5 cases in which the disease became chronic had this level of renal function been reached at that time.

It is my belief, based on clinical observation in these cases of nephritis and on study of the records, that if the delay in the rise of urea clearance is explained by the presence of clinically evident infection or by circulatory failure the danger of incomplete healing of the nephritis is less than if no such cause for the delayed rise can be found.

The bad prognostic significance of slow recovery from the acute stage of nephritis was noted by Van Slyke and his co-workers,[6] who wrote:

> The duration of the acute stage, in our cases which recovered or improved to the latent state, varied from 4 to 15 months. Noticeable improvement *began* within 4 months, in all cases that were not destined to pass into the chronic or terminal stages.

The results of observations in my cases indicates that one may pick out the cases in which the disease is most likely to become chronic within the first two months of the illness or sometimes even in the first month, by observing the rate of recovery of renal function, as indicated by successive urea clearance tests done at short intervals. Van Slyke and his co-workers[7] stated: ". . . . we can not conclude that maintenance of normal renal function during the first months of the acute stage justified either a good or bad prognosis." These observers had studied 23 cases of nephritis in the acute stage. My experience, based on the cases discussed in this paper, differs from that of Van Slyke and his associates. In none of my cases in which normal or nearly normal renal function was maintained or was regained early during the acute stage is the nephritis known to have failed to heal. It is true, however, that in 1 case in which the patient early regained normal renal function there was residual albuminuria. An analysis of the series of 188 cases of hemorrhagic nephritis observed in the Strong Memorial and Rochester Municipal Hospitals between 1926 and 1939 will now be presented. I shall first make use of the fact that it has been demonstrated that in the cases in which recovery occurred

6. Van Slyke, D. D., and others: Observations on the Courses of Different Types of Bright's Disease, and on the Resultant Changes in Renal Anatomy, Medicine **9**:257, 1930 (pp. 277-279).

7. Van Slyke and others,[6] p. 285.

there was a rapid rise of renal function during the acute stage, if, indeed, the renal function had been much impaired, and that in the cases in which the disease became chronic there was a slow recovery of renal function. From consideration of these facts, it is evident that if a patient with hemorrhagic nephritis is progressing toward recovery, there usually would be no reason for admitting him to the hospital at any considerable time after the onset of the nephritis. For purposes of comparison, the cases are divided into three groups: those in which the patient was admitted within one month of onset of the nephritis (or in which the nephritis developed while the patient was in the hospital), those in which the patient was admitted more than one month after onset of the nephritis and those in which the duration of the nephritis was never satisfactorily determined. The distribution of the cases

TABLE 2.—*Time of Admission to Hospital and Outcome in One Hundred and Eighty-Eight Cases of Nephritis*

Outcome	Patient Admitted in First Month of Nephritis		Patient Admitted After First Month of Nephritis		Duration of Nephritis Uncertain	
	Boys	Girls	Boys	Girls	Boys	Girls
Patient recovered	60	41	1	0	2	0
Outcome uncertain	24	16	0	1	0	0
Residual albuminuria	3	1	0	0	0	0
Patient died in acute stage	11	1	0	0	0	0
Chronic nephritis	5	2	12	7	0	0
Hypertension without nephritis	0	0	0	1	0	0
Total	103	61	13	9	2	0

according to time of admission and outcome of the nephritis is shown in table 2.

It is obvious from the large number of patients with chronic nephritis among those admitted to the hospital more than one month after the onset of their disease that this group is a selected one, selected because they had not tended to recover. No less than 9 of the 19 patients had had the disease for a year or more before their first admission to the hospital. The disease of 3 of these was in the terminal stage (Van Slyke and co-workers [6]) when they were admitted, as was that of 3 others who had had the disease for less than a year before their admission. It is clear from examination of the records that 17 of these 19 patients with chronic nephritis came to the hospital because their disease had not shown a tendency for the rapid improvement which is characteristic of those cases of acute nephritis in children in which recovery occurs. Of the patients admitted more than a month after the onset of their illness, the only one known to have recovered was a boy of 12 years who had been treated at another hospital for acute nephritis five months before and who came to this clinic chiefly because of pains in the joints and

obesity. His urine then contained albumin and microscopic blood. Four years later his urine contained no albumin and the sediment was normal.

In view of the fact that in the cases of the 2 patients for whom the time of onset of nephritis could not be determined satisfactorily but who recovered the course was similar to that in the majority of other cases of acute nephritis in which recovery ensued, it seems probable that the patients were admitted early in the course of the nephritis. For this reason it seems permissible to include their cases with the 164 cases in which the patient was known to have been admitted to the hospital within a month of the onset of the nephritis and to base any discussion of the course and prognosis of acute nephritis on these 166 cases. Of the patients in these 166 cases, 103 (62 per cent) were boys and 63 (38 per cent) girls. Scarlet fever is known to have occurred immediately before the nephritis in 35 of the 103 cases in which the patient recovered, in 11 of the 40 of uncertain outcome, in 1 of the 4 in which there was residual albuminuria, in 1 of the 7 in which the disease became chronic and in 6 of the 12 in which the patient died in the acute stage of the disease.

CAUSES OF DEATH IN THE CASES OF FATAL OUTCOME

In 12, or 7.2 per cent, of 166 cases of acute nephritis the patient died. Three of the 12 patients were infants, aged 3, 4 and 11 months. None of the patients under 1 year of age survived the acute stage. Two of these infants are known to have had septicemia due to hemolytic streptococci, and 1 of these had meningitis. One infant, aged 16 months, had cleft palate, tetany and possibly meningitis. This was the only 1 of 4 infants in the second year of life who died. One child 2½ years of age had septicemia due to a pneumococcus and another, 4 years old, had septicemia due to hemolytic streptococci, so that 4 of the 12 patients who died had septicemia. Three children died of cardiac failure and 2 of cardiac failure together with convulsions. Three of these 5 patients with cardiac failure died within one day of their admission to the hospital, with the severe symptoms which had caused them to be brought to the hospital. One patient had anuria lasting several days, with a low level of plasma chlorides, and at autopsy acute suppurative peritonitis was present. Of the 12 deaths, 5 could well have been due to the acute diseases of which the nephritis was a complication and 7 appeared to be due to the nephritis. It will be seen that the causes of death are infection (sepsis), cardiac failure and hypertensive encephalopathy, and in 1 case anuria caused by a lowering of the level of plasma chlorides appeared to be of great contributory importance.

Anuria Due to Loss of Chloride.—Little attention has been paid to the cause of oliguria or anuria in cases of acute nephritis. Higgins and

Graf [8] reported the case of a girl of 3½ years who had acute nephritis complicating scarlet fever and who was anuric for more than seven days. While there is no report of any determination of the level of plasma chlorides in this case, it is of interest that the formation of urine was resumed after 9 Gm. of sodium chloride in a 2 per cent solution was given in two intravenous injections in one day.

Van Caulaert and Pétrequin [9] reported low levels of chlorides in the blood in all cases of acute nephritis without edema in which there was anuria or marked oliguria. Bindschedler and Haubtmann [10] reported the case of a child with acute nephritis in which the plasma chlorides were lowered to 70 milliequivalents per hundred cubic centimeters and the oliguria and general clinical condition responded dramatically to the administration of sodium chloride. Cassoute, Poinso and Capus [11] observed a similar case, in which there were no studies of the blood chlorides, in which the patient responded well to the giving of sodium chloride by vein and by mouth. Because of the infrequency of reports showing the importance of the depletion of chlorides, brief abstracts of 2 cases are given here.

CASE 1.—S. H., an 8 year old white boy, was admitted to the hospital Aug. 1, 1931 with acute nephritis of seven days' duration complicating scarlet fever. Anorexia and vomiting had been present since the onset of the nephritis, and marked oliguria had been present for six days before admission. On admission the level of plasma chlorides (as sodium chloride) was 468 mg., or 80 milliequivalents, per hundred cubic centimeters; three days later it was 398 mg., or 71 milliequivalents, and the following day 421 mg., or 75 milliequivalents, with the carbon dioxide-combining power of the blood 30 volumes per cent at the time of the last determination of plasma chlorides. He had not voided during the two days after admission; so he was catheterized, and 30 cc. of urine was obtained. Chlorides were not given, the formation of urine was not resumed and the child died on August 7, thirteen days after the onset of nephritis and eleven days after the onset of marked oliguria. Autopsy showed suppurative peritonitis.

CASE 2.—A. S., a 10 year old white girl, was admitted Aug. 6, 1936 with acute nephritis of three days' duration. The day after admission a test showed that the urea clearance was 1.6 per cent of normal for each of two periods of four and five hours (the lowest level of renal function which I have encountered in a case

8. Higgins, H. L., and Graf, W. J.: Anuria of Seven Days' Duration in a Child with Scarlet Fever, Am. J. Dis. Child. **33**:926 (June) 1927.

9. van Caulaert, C., and Pétrequin, P. S.: Étude physio-pathologique, pathogénique et thérapeutique de hypochloruration, Arch. d. mal. d. reins **6**:52, 1931.

10. Bindschedler, J. J., and Haubtmann, P.: Syndrome d'azotémie par manque de sel au cours d'une néphrite aiguë chez un enfant de 4 ans, Strasbourg méd. **93**: 283, 1933.

11. Cassoute; Poinso, R., and Capus, J.: Anurie an cours d'une néphrite aiguë chez un enfant de 4 ans. Échec des divers traitements. Rétablissement de la diurèse par le sérum salé hypertonique intra-veineux, Bull. Soc. de pédiat. de Paris **31**:109, 1933.

of acute nephritis). A search began for an explanation of the low urea clearance and the oliguria. Vomiting one to three times a day had occurred for four days. The level of nonprotein nitrogen in the blood on August 8 was 120 mg. per hundred cubic centimeters, and that of chlorides in the plasma was 497 mg. (85 milliequivalents). The urinary output for the day before had been 125 cc. On the afternoon of August 8, 20 and 26 cc. of a 15 per cent solution of sodium chloride, a dose calculated to raise the plasma chlorides to normal, was given intravenously. The urinary output for that day (ending at 7 a. m. on August 9) was 475 cc., and the output for the subsequent two days was 800 and 1,175 cc. On August 10 the level of chlorides in the plasma was 550 mg. per hundred cubic centimeters (94 milliequivalents) and on August 11 630 mg. (109 milliequivalents). On August 9 the urea clearance was 8 per cent of normal, and on August 13 it was 16 per cent of normal. When last seen, one year later, the child had recovered, except for slight residual albuminuria.

In at least 2 more cases in this series oliguria seemed to be due to loss of chlorides, but the observations are not as striking as in the 2 cases cited. It seems that in all cases of acute nephritis without gross edema and with oliguria or anuria the level of plasma chlorides should be determined and sufficient sodium chloride given to restore them to the normal level and to maintain them there. Clausen and Ringsted [12] have recently shown that in cases of pyloric stenosis (in adults) marked reduction of the urea clearance, to as little as 5 per cent of normal, with chloropenia and dehydration, may occur without its being possible by clinical means to estimate the degree of dehydration. If loss of chlorides has such effects on persons with normal kidneys, it is even more necessary that the loss be detected and corrected in such cases of nephritis as the ones cited.

COURSE OF HEMORRHAGIC NEPHRITIS

Of 166 patients with acute nephritis admitted to the hospital early in the course of their disease, 154 survived. Of these, 103 are considered to have recovered from their nephritis. Seventy of these had normal Addis counts on the urinary sediment a year or more after the onset of the disease. In the cases of 33 other children, a diagnosis of recovery was made on the basis of one or more examinations of the urine by the usual technic. Only 17 of the 103 patients considered to have recovered were followed for less than two years from the onset of the nephritis.

Four children (3 boys and 1 girl) were found after a year, one year and eight months, two years and three years and nine months to have residual albuminuria, with normal urinary sediment as judged by the Addis technic. One of these patients was observed three years after the onset of the nephritis, during an attack of otitis media caused by

12. Clausen, J., and Ringsted, A.: On Pre- and Post-Operative Fluid Treatment in Pyloric Stenosis, Acta chir. Scandinav. **82**:365, 1939.

hemolytic streptococci and lobar pneumonia due to Pneumococcus type I; Addis counts disclosed no abnormality of the urinary sediment. In 3 of the 4 cases in which there was residual albuminuria, as may be seen in table 1, the recovery of normal renal function appears to have been distinctly slow. This fact, in addition to the low average level of renal function (chart 2) present early in these cases, seems to place them in a rather close relation to cases of latent or chronic nephritis.

In the group of 40 cases in which the outcome was uncertain are included 6 cases in which the duration was less than a year.

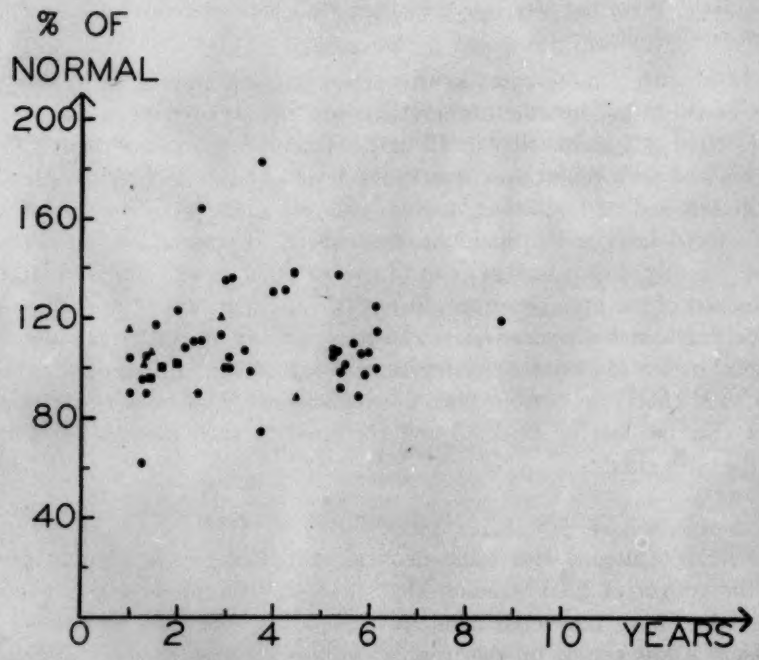

Chart 3.—Level of urea clearances of 50 patients who had had acute nephritis one year or more after onset. The triangles indicate patients whose disease became chronic (5), the circles patients who recovered (42) and the squares patients who had residual albuminuria (3).

In chart 3 are shown the levels of renal function in 42 cases in which the patient recovered, in 5 in which the disease became chronic and in 3 in which there was residual albuminuria, determined more than one year after the onset of the nephritis. It will be observed that the level of renal function was apt to be normal in each of these groups of cases. In only 2 of the cases in which recovery ensued was the urea clearance below 80 per cent of normal. In 1 it was 74 per cent of normal two years and nine months after the onset of nephritis. For 1 child, a girl who was 11 years old at the onset of nephritis, in 1938, three

determinations made one year and three months later showed urea clearances of 69, 51 and 68 (an average of 63) per cent of normal. It is of interest that she was 1 of 3 patients mentioned earlier for whom the diagnosis in the acute stage was based on what might be called "minimal evidence."

In 7 cases observed first while the nephritis was in the early acute stage the disease is considered to have progressed to the chronic stage. Since, as Lyttle [13] noted, cases in which nephritis progresses from the acute to the chronic stage are rarely observed, it is desirable to present brief abstracts of the records of these cases.

CASE 3.—In C. W., a girl who was born in 1913, acute nephritis developed in 1926; she was admitted to the hospital a week later. She recovered slowly and was left with a tendency to slight edema, headache, dizziness, nausea, fatigability and dyspnea on exertion. For several months the urine showed a tendency to become clear of albumin and sediment, but two and a half years after onset she had moderate to heavy albuminuria, microscopic hematuria, headaches, general malaise and abdominal pain, with normal blood pressure. She has not been seen since 1928.

CASE 4.—In D. C. B., a girl who was born in 1916, acute nephritis developed as a complication of severe streptococcic tonsillitis in April 1929. Ten days after onset she was admitted to the hospital, where she remained for two months. Edema, ascites, tachycardia, cardiac enlargement, hypertension and passive congestion of the lungs were present during the acute stage. Tonsillectomy was performed six weeks after onset of the nephritis. The blood pressure never returned to normal for any appreciable period. The urine continued to show a small amount of albumin. Two years after onset the urea clearance was 94 per cent of normal and a year later 104 per cent of normal. In 1935, during pregnancy, she had hypertension (a blood pressure of 140 mm. of mercury systolic and 88 mm. diastolic), headache, blurring of vision and frequency and urgency of urination. Urea clearances were about 80 per cent of normal. The urine showed 4 to 6 Gm. of albumin per thousand cubic centimeters and the sediment 9,000,000 to 30,000,000 red cells per twelve hour period, as determined by the Addis technic. Premature separation of the placenta necessitated cesarean section and hysterectomy. Efforts to study the patient further have been unsuccessful.

CASE 5.—In F. A., a youth born on Sept. 7, 1919, acute nephritis developed as a complication of a cold and sore throat in November 1931. Generalized edema, frequent vomiting, oliguria, hematuria, widespread petechiae and otorrhea were present on admission. The nonprotein nitrogen content of the blood was 200 mg. per hundred cubic centimeters. Cardiac failure and orthopnea, with a maximum blood pressure of 198 systolic and 144 diastolic, developed. The cardiac failure responded almost dramatically to the administration of digitalis. Successive urea clearances are shown in *D* of table 1. More than three months after onset the urea clearance was only 60 per cent of normal. In March 1934 this boy showed good physical development, with no symptoms of nephritis. The blood pressure was 125 to 130

13. Lyttle, J. D.: The Treatment of Acute Glomerulonephritis in Children, Bull. New York Acad. Med. **14**:212, 1938.

mm. of mercury systolic and 95 mm. diastolic. Clinical and roentgen examinations showed that the heart was enlarged to the left. The Addis count showed 400,000 red cells, 1,030,000 leukocytes and epithelial cells and 16,000 casts. The urine contained a trace of albumin. The urea clearance was then 120 per cent of normal. The patient is a delinquent, and further efforts to study him have been in vain.

CASE 6.—In L. S., a youth born on June 26, 1920, acute nephritis developed as a complication of a sore throat in November 1934. In 1932, after an injury, he contracted scarlet fever, for which he was hospitalized, but the urine remained normal throughout this illness. The acute nephritis was characterized by moderate generalized edema, sore throat, persistent low grade fever, hypertension and gross hematuria. The serum proteins were reduced to a level of 4.6 Gm. per hundred cubic centimeters (albumin, 2.08 Gm., and globulin, 2.52 Gm.) on admission, four days after the apparent onset of the nephritis. Five weeks after admission the serum proteins had risen to a level of 6.16 Gm. per hundred cubic centimeters (albumin, 4.17 Gm., and globulin, 1.99 Gm.). Albuminuria and microscopic hematuria were still present on discharge, five months after onset. The albumin persisted through 1936 and 1937. In May 1939, four and one-half years after onset, a specimen of urine collected by the technic of Addis measured 175 cc., contained 0.1 Gm. of albumin per thousand cubic centimeters and had a specific gravity of 1.032. A count of the sediment showed 39,000 casts, 1,575,000 red cells and 612,500 leukocytes and epithelial cells. At this time the urea clearance was 88 per cent of normal. He was at that time clinically well. His successive urea clearances are shown in *D* of table 1.

CASE 7.—P. M., a boy who was born on April 11, 1924, was admitted to the hospital because of acute rheumatic fever in April 1935. He had had rheumatic fever since the age of 3 or 4 years, and he also had mitral and aortic insufficiency. He had recently been exposed to scarlet fever. On admission the urine was normal. Fifteen days later there developed severe acute nephritis, with cardiac failure, and the nonprotein nitrogen content of the blood was 281 mg. per hundred cubic centimeters. The urea clearances during the acute stage are shown in *D* of table 1. In February 1936, after an infection of the throat, gross hematuria developed and the urea clearance was reduced to 34 per cent of normal, from which level it rose to 82 per cent of normal in three months. Microscopic hematuria continued through 1938, but in 1939 four examinations of the urine showed a trace of albumin as the only abnormality. The last urea clearance, determined on Aug. 2, 1938, was 104 per cent of normal.

CASE 8.—In M. F., a boy who was born on Aug. 5, 1929, acute nephritis developed in November 1937 after an infection of the upper respiratory tract. Before the onset of the nephritis he was thought to have mild rheumatic fever. Anorexia, headache, vomiting, gross hematuria and mild anemia, but no edema, were present in the early acute stage. The levels of serum proteins on admission were: albumin, 3.5 Gm. and globulin, 1.94 Gm. per hundred cubic centimeters. He was kept continuously in bed in the hospital, but he continued to have a small to moderate amount of albumin in the urine, with abnormal numbers of red cells and casts. In June 1938, while he was still in bed in the hospital, an acute infection of the respiratory tract, with a rise in temperature to 40 C. (104 F.), developed. This was followed by gross hematuria and a fall of the urea clearance to 42 per cent of normal, from which level it rose to 87 per cent of normal

in two months. In November 1939, he continued to have albuminuria and microscopic hematuria, but he attended school and felt well. There are no known foci of infection.

CASE 9.—J. De S., a boy born on Jan. 19, 1923, was admitted in January 1938 with acute nephritis complicating an infection of the upper respiratory tract. Gross edema, gross hematuria and oliguria were present. The levels of serum proteins three days after onset were: albumin, 2.75 Gm., and globulin, 1.81 Gm. per hundred cubic centimeters. He had bilateral suppurative otitis media, caused by pneumococcus type XXX. The blood stream was invaded by the same organism. Early in the course of the nephritis clinical and roentgen examinations showed that he had acute antral sinusitis, but operation was delayed for fear of aggravating his nephritis at a time when his renal function was low. The sinusitis had cleared by the time the operation could have been performed safely. *D* of table 1 shows the level of urea clearance during the acute stage of the disease. Tonsillectomy, performed two and one-half months after the onset of the nephritis, resulted in a transitory aggravation of the albuminuria and hematuria. He was hospitalized for three and one-fourth months. Sixteen months after onset the urea clearance was 106 per cent of normal. The systolic blood pressure was 100 mm. of mercury and the diastolic 65 mm.; the Addis count showed 23,000 casts, 4,200,000 red cells and 3,600,000 white cells. He had no symptoms of nephritis.

The question of selection of cases arises even with cases in which the patient was admitted to the hospital early in the course of the nephritis. It has been my clinical impression that in the cases in which the acute nephritis progressed to the chronic stage the acute stage is more apt to have been severe than in the cases in which recovery ensued. Examination of the histories of these 7 cases of acute nephritis in which the disease became chronic raises the question whether in 3 of them the patient would have come to the hospital had the symptoms not been severe. One manifestation of nephritis which cannot fail to impress the family and the physician is the occurrence of much edema. Since Van Slyke and his associates [14] have shown that lowering of the level of plasma proteins in cases of acute nephritis may indicate a poor prognosis for recovery and since Rennie [15] has shown that the severity of edema in cases of acute nephritis can be correlated with the degree of lowering of the plasma proteins, it follows that the occurrence of much noncardiac edema is indicative of a less favorable prognosis than if there is not so much edema. Other alarming symptoms of acute nephritis which might lead to hospitalization of a patient are convulsions, severe cardiac failure and anuria.

To discover whether there might have been a selection of cases in the group of 154 in which the patient survived the acute stage, the incidence of one or more of the four previously mentioned severe manifestations of the disease was determined from the case histories.

14. Van Slyke and others,[6] p. 296.
15. Rennie, J. B.: Oedema in Nephritis, Quart. J. Med. **2**:521, 1933.

In 22 of 103 cases in which recovery ensued, in 13 of 40 cases in which the outcome was uncertain, in 2 of 4 cases in which there was residual albuminuria and in 5 of 7 cases in which the disease became chronic, one or more of these manifestations was present. I believe that these figures indicate that there was a selection of cases even in the small group in which the nephritis became chronic.

COMMENT

Other investigators have tried to evaluate the influence of the factor of case selection on the gross incidence of chronicity in series of cases of hemorrhagic nephritis. Richter [16] reported on the outcome in 160 cases of hemorrhagic nephritis in persons above the age of 13 years. In 60 of these the disease was considered to be chronic when the patient was first seen. In 10 the patient died in the acute stage of the disease. Of the remaining 90 cases, the outcome could be determined in 77, in 15, or 19.5 per cent, of which the disease had become chronic. He also observed 2 cases in which there was hypertension ten and nineteen years later, without evidence of chronic nephritis.

I have observed 1 case in which there was hypertension, without nephritis, some years after the onset of nephritis. The patient, a girl of 11 years, was seen in 1926, four months after the onset of generalized edema, headache, dizziness, nocturia and massive albuminuria. Hematuria was never observed. The disease at that time was believed to be nephrosis. That such confusion can easily occur is evident from the statement of Van Slyke and his associates: [6]

> The one phase of the "hemorrhagic" disease which is not hemorrhagic is encountered during improvement or recovery from the acute disease. The hematuria may completely disappear while there is still heavy proteinuria, albumin deficit in the plasma, and some tendency to edema. There follows then a period of some weeks or months during which such a case is indistinguishable, except for its history, from a pure nephrosis.

The fact that the blood pressure was 132 mm. of mercury systolic and 92 mm. diastolic in 1928 and 138 mm. systolic and 90 mm. diastolic in 1937, two and a half and eleven years, respectively, after onset, indicates that the patient probably had hemorrhagic nephritis when first seen. Winkenwerder, McLeod and Baker [17] wrote:

> With few exceptions, the patients classified (according to the criteria of Addis) as either well or in the latent phases of nephritis were seen within a few days to a few weeks after the apparent onset of their disease, while a few acquired

16. Richter, A. B.: Prognosis in Acute Glomerular Nephritis, Ann. Int. Med. **9**:1057, 1936.

17. Winkenwerder, W. L.; McLeod, N., and Baker, M.: Infection and Hemorrhagic Nephritis, Arch. Int. Med. **56**:297 (Aug.) 1935.

the disease while they were under observation. On the other hand, several of the patients whose nephritis was in the progressive stage or had terminated fatally were seen months and sometimes years after the alleged onset.

My experience has been entirely in agreement with the observations of Richter [16] and of Winkenwerder and his associates,[17] in that most patients with chronic nephritis are likely to have had the disease for a long time before coming to the hospital. Some, to be sure, had been seen previously in other hospitals.

It will be seen that of the 114 cases of acute nephritis in which the patient survived the acute stage and in which the outcome is known, in 7, or 6.1 per cent, the disease became chronic in 4, or 3.4 per cent, there was residual albuminuria and in 103, or 90.5 per cent, recovery ensued. If one accepts the idea that these cases of less favorable outcome are in part selected cases, the prognosis of acute nephritis in children must be considered to be even more favorable than these figures indicate.

One impressive fact about the 7 cases of acute nephritis in which the disease became chronic is that in each instance the nephritis has been less rapidly progressive than in most cases of chronic nephritis in which the disease is well established at the time of admission to the hospital. The reasons for this are not entirely clear. One wonders if a dietary factor might be of importance. Aldrich [18] reported that children with chronic nephritis were greatly improved by eliminating the restriction of protein and giving a full diet. Alving [19] reported that the recovery from acute nephritis may be retarded by restricting the intake of protein. Keutmann and McCann [20] have shown that adults with nephritis recovered more rapidly and more surely if they were given a liberal allowance of protein. Of my cases of chronic progressive nephritis in which the disease was well established on admission, in only about half was there a definite history of restriction of dietary protein by the physician. Anorexia caused by the disease may have had the same result in other cases.

For the greater part of the time covered by this study, in the cases here reported, no restriction of dietary protein has been imposed on patients with any stage of nephritis when there was no evidence of nitrogen retention. The children have been kept in bed, whenever possible, until albuminuria and hematuria subsided. Foci of infection have been treated by accepted methods.

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18. Aldrich, C. A., in discussion on Thomas, W. A.: Source and Rôle of Urinary Protein in Nephritis, J. A. M. A. **97**:1055 (Oct. 10) 1931.

19 Alving, A. S.: The Diet in Chronic Bright's Disease, M. Clin. North America **17**:1195, 1934.

20. Keutmann, E. H., and McCann, W. S.: Dietary Protein in Hemorrhagic Bright's Disease, J. Clin. Investigation **11**:973, 1932.

SUMMARY

The level of renal function, as indicated by a single determination of the urea clearance, is of little prognostic value. The trend of successive tests at short intervals is of great value in indicating whether recovery will probably ensue or whether the nephritis is likely to become chronic.

Cases in which the patient is admitted to the hospital late in the course of acute nephritis or later are selected cases and must be excluded in any consideration of the prognosis of acute nephritis. Even then, there will remain some case selection; patients with the more severe forms of the disease are more apt to come to the hospital, and their disease is more likely to become chronic.

Of 114 cases of early acute hemorrhagic nephritis, in 7, 6.1 per cent, the disease became chronic, in 4, or 3.4 per cent, there was residual albuminuria and in 103, or 90.5 per cent, recovery ensued. The ultimate significance of the "residual albuminuria" remains to be determined.

IX. A ROENTGENOGRAPHIC CEPHALOMETRIC APPRAISAL OF UNTREATED AND TREATED HYPOTHYROIDISM

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REVIEW OF THE LITERATURE

This is a report on craniofacial growth in children with thyroid deficiency. It is the purpose of this study to indicate the deviations from normal growth which occur and to point out the efficacy of thyroid therapy in inducing developmental progress in the craniofacial areas. It is hoped that the use of a roentgenographic cephalometric technic in the study of abnormal growth will yield some additional information concerning normal developmental progress.

Thoma,[1] in reviewing the literature on the craniofacial changes in cretinism, stated that characteristic alterations are found in the skull bones, the jaws and the teeth. He cited a number of cases reported by Kranz, Meyerhofer and Knaggs.

Knaggs, in describing an 18 year old cretin, wrote:

> The face looked mean, chiefly owing to the shortening of its upper part. The root of the nose lay farther back than usual and the frontal bone inclined considerably forward above it. The upper jaw protruded, the arch of the palate was absent and the alveolar process was broad and high. The two halves of the jaw were completely separated and the angles were slightly marked. Nearly all of the milk teeth were carious and the permanent ones seemed to be struggling for the necessary room to develop.

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This paper is based on a thesis submitted by Dr. Engel to the faculty of the Graduate School of the University of Illinois in partial fulfilment of the requirements for the degree of Master of Science in Orthodontia.

1. Thoma, K. H.: Clinical Pathology of the Jaws, Springfield, Ill., Charles C. Thomas, Publisher, 1934.

Taylor and Appleton [2] reported that in their case the cranium was normal and the mandible conspicuously retarded in development. Wolf [3] pointed out:

> In the endemic form of cretinism the skull is brachycephalic in shape while in the sporadic group it is generally dolichocephalic. Most of the characteristic deformities of the skull, i. e., abnormalities of the face, nose and fontanelles can be explained partially by the delayed growth of cartilage between them. In either case the nasal bones and nasal processes of the superior maxillae are not pushed sufficiently forward and a characteristically depressed nasal bridge results.

Fisk [4] expressed the belief that atypical class III malocclusions with retardation in maxillary and carpal development may be attributed to hypothyroidism. Zuck [5] expressed the belief that retardation induced by any experimental procedure or any clinical defect such as hypothyroidism results in underdevelopment of the face. In 1 of the cases which he reported lack of development was especially marked in the maxilla. The respiratory area (the area between the nasion and the anterior nasal spine) was poorly developed and the palate narrowed. These abnormalties were undoubtedly involved in the production of malocclusion in this case. He reported that some facial growth was associated with therapy.

Benda [6] stated that from the anatomic point of view the vault of cretins is always large and the circumference of the skull is normal or even greater than normal but the base is small. He pointed out that the cartilaginous spaces are larger than normal and that pathologic changes occur in the chondral sites.

Retardation of the eruption of the teeth in children with hypothyroidism has been noted by many observers.[7]

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2. Taylor, G. L., and Appleton, J. L. T.: The Dental Aspects of a Case of Dwarfism (Cretinism?), Dental Cosmos **71**:124, 1929.

3. Wolf, W.: Endocrinology in Modern Practice, Philadelphia, W. B. Saunders Company, 1937.

4. Fisk, G. V.: The Treatment of Incipient Class III Malocclusion, Am. J. Orthodontics **25**:518, 1939.

5. Zuck, T. T.: The Measurement of Aberrant Developmental Growth, J. Pediat. **3**:424, 1933.

6. Benda, C. E.: Growth Disorder of the Skull in Mongolism, Am. J. Path. **16**:71, 1940.

7. (*a*) Engelbach, W.: Endocrine Medicine, Springfield, Ill., Charles C. Thomas, Publisher, 1932. (*b*) Thoma.[1] (*c*) Canelo, C. K., and Lisser, H.: Two Cases of Childhood Myxedema, Endocrinology **19**:21, 1935. (*d*) Kerley, C. S.: Subthyroidism with Defective Dental Development, Arch. Pediat. **55**:548, 1938. (*e*) Wolf.[3] (*f*) Bronstein, I. P.: Unpublished data.

Several experimental studies on hypothyroidism have been concerned with growth in the craniofacial area. Dye and Maughan [8] made a study of the bone growth of 4 dogs which had been thyroidectomized at an early age. They found that the bone changes consisted of retardation in length and epiphysial growth, with diminished weight and volume. They expressed the belief that the changes were confined to endochondral bone (epiphysial plates) and did not appreciably affect subperiosteal and membranous bone. The length of the upper part of the face was decreased relatively more than the other measurements. The width of the face was the same as that of the controls or greater. Their data on skull growth were similar. They found that growth in length of the skull was most susceptible to interference, that growth in height was next and that growth in breadth was least easily affected. In their small series the differences between the controls and the experimental animals were not sufficient to warrant acceptance of the conclusions. Liddell [9] studied the skulls of thyroidectomized sheep. He reported that the skull was foreshortened and disproportionately wide and that the ossification of the basisphenoid-basioccipital junction was incomplete.

The most significant work is that of Todd and Wharton [10] and Todd, Wharton and Todd.[11] They studied the skull growth of a group of sheep which had been thyroidectomized at ages of from 1 to 3½ months.[12] Since the development of the brain case of the sheep is practically complete at 1 month of age, the disturbance of growth was not reflected in that structure. However, the eruption of the teeth was delayed and the facial growth suffered. The upper part of the face, the respiratory area and the maxillary tuberosity were the next most susceptible to disturbance in growth. The defect in the growth of the maxillary tuberosity was undoubtedly associated to a considerable degree with the retardation in the eruption of the teeth. The upper part of the face was particularly affected in the development of the nasal and the frontomalar-lacrimal complex. There was also some deficiency in the development of the frontal process of the maxilla and the premaxilla. The authors stated: "The result is a cramped, ill-developed snout, a juvenile steep forehead and an upcurving of the hard palate."

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8. Dye, J. A., and Maughan, G. H.: Further Studies of the Thyroid Gland, Am. J. Anat. **44**:331, 1929.

9. Liddell, H. S.: The Growth of the Head in Thyroidectomized Sheep, Anat. Rec. **30**:327, 1925.

10. Todd, T. W., and Wharton, R. E.: The Effect of Thyroid Deficiency on Skull Growth in the Sheep, Am. J. Anat. **55**:97, 1934.

11. Todd, T. W.; Wharton, R. E., and Todd, A. W.: The Effect of Thyroid Deficiency upon Bodily Growth and Skeletal Maturation in the Sheep, Am. J. Anat. **63**:37, 1938.

12. The Western Reserve craniostat was used for measurement and tracing.

The adjustment, or hafting, zone (palatomaxillopterygoid) was apparently not affected, and the face, though not completely thrust downward, underwent the characteristic buckling in the cranial base. The progress of suture closure was retarded. Mandibular growth remained unaffected.

One animal which was thyroidectomized at 42 days of age, then was fed 0.1 mg. of thyroxin per day for two months and was killed when 22 months old showed development of the anterior portion of the maxilla and the frontal bones which had not progressed beyond that usual for an animal 4 months of age, while other facial areas remained retarded in growth. Todd expressed the belief that despite the administration of thyroxin the "scar" remained. The evidence for this conclusion seems insufficient.

Ziskin, Salmon and Applebaum [13] thyroparathyroidectomized rats at birth and at 7 days of age. They reported that the weight of the mandible and the area of the maxillary arch were less than normal. The eruption of the molars was delayed, and the development of dentin and roots was retarded.

MATERIAL AND METHOD

This report is based on an intensive study of 13 selected cases of hypothyroidism from a series of 27 classic cases. The diagnosis of thyroid deficiency was thoroughly established on the basis of the history, the physical examination, a roentgenographic assessment of osseous development (particularly of the carpal centers of ossification and of the status of epiphysial closure), the values for blood cholesterol and the physical and mental progress with thyroid medication. Determination of the basal metabolic rate was attempted routinely; nevertheless, great reliance could not be placed on the results because of the difficulty in obtaining cooperation.

Cephalometric roentgenograms were made of each patient, with the technic developed by Broadbent.[14] The lateral roentgenogram was traced, and a comparison was made between the roentgenograms of treated and those of untreated persons of approximately the same age. This was done graphically by means of the method of superposition described by Broadbent. Craniofacial landmarks were established, and linear and angular measurements involving these points were taken, with the aid of correctional scales [15] and a protractor. These points are illustrated in figure 1, and measurements for the subjects studied are given in table 1. The exact location of the points has been defined by Brodie.[16] (One additional measurement,

13. Ziskin, D. E.; Salmon, T. N., and Applebaum, E.: The Effect of Thyroparathyroidectomy at Birth and at Seven Days on Dental and Skeletal Development, J. Dent. Research **19**:93, 1940.

14. Broadbent, B. H.: A New X-Ray Technique and Its Application to Orthodontia, Angle Orthodontist **1**:45, 1931; The Face of the Normal Child, ibid. **7**:183, 1937.

15. Adams, J. W.: Correction of Error in Cephalometric Roentgenograms, Angle Orthodontist **10**:3, 1940.

16. Brodie, A. G.: On the Growth Pattern of the Human Head from the Third Month to the Eighth Year of Life, Am. J. Anat. **68**:209, 1941.

the length of the nasal bone, was obtained by measuring from the nasion to the tip of the nasal bone.)

To facilitate visualization and interpretation the superposed tracings were broken down into straight lines, and a quadrangular figure was formed by connecting the points, *S, N, NS, 1, $\overline{1}$, GN* and *GO*. The nasal floor, *NS-PNS*, was also indicated. The composite method eliminates confusion and brings out clearly a number of salient features.

Comparison of the material for subjects with hypothyroidism with that for the normal controls is at present in a preliminary stage, since the normal subjects in the series studied and reported on by Brodie [16] ranged from 3 months to 8 years of age, while the ages for the cretin group extended to 23 years. The means of

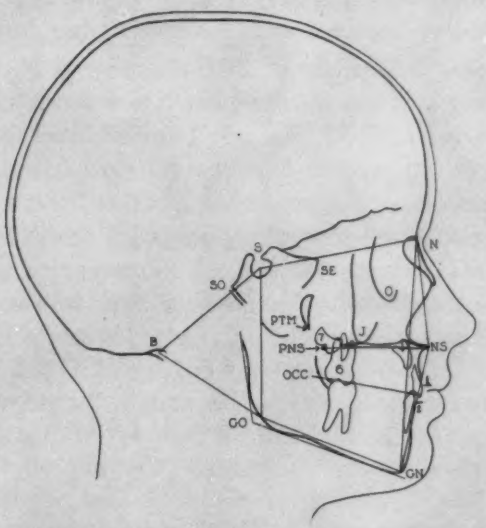

Fig. 1.—Tracing of a lateral roentgenogram, showing the location of the craniometric landmarks and planes used. *B* signifies Bolton's point; *GN*, gnathion; *GO*, gonion; *J*, jugal process; *N*, nasion; *NS*, anterior nasal spine; *O*, orbitale; *OCC*, occlusal plane; *PNS*, posterior nasal spine; *PTM*, ptergomaxillary fissure; *S*, center of sella turcica; *SE*, sphenoethmoid junction; *SO*, spheno-occipital junction; *7*, maxillary second molar, and *6*, maxillary first molar.

the measurements for the normal controls were tabulated with those of the cretins under investigation.

Carpal ossification was roentgenographically determined, and data on this subject were tabulated as given in the roentgenographic reports. It would have been better to have indicated in all cases the number of carpal centers of ossification present rather than to have attempted to evaluate the ossification age, but, unfortunately, a number of the roentgenograms were not available for reassessment. Examination of the carpal areas as revealed in roentgenograms of the hand and wrist is of service in studying the stages of maturation in epiphysial ossification,

TABLE 1.—*Linear and Angular Measurements for Normal Children and for Children with Treated and Untreated Hypothyroidism*

Subject	Age	Treatment Record	Linear Measurements, Mm.											Angular Measurements, Degrees							
			S-N	S-B	B-N	Skull Length	N-NS	N-1	N-GN	GO-GN	S-GO	B-NS	NS-PNS	Nasal Bone	S-N-1	S-N-NS	S-N-GN	S-N-OCC	N-GN-GO	N-S-GO	S-GO-G-N	N-NS-PNS	B-S-N
Control	1 yr.	.....	54.5	45	95.5	164.5	32.1	49.2	77.2	43.7	46.2	..	37.2	14.3	79	87	70.1	....	72.2	97	119.5	86.5	145.5
D. V.	1 yr. 3 mo.	Began at 3 mo. of age, active since referral	50.5	48	93.5	161	29	45	....	42	....	92	38.5	13	89	95.5	....	....	....	....	.....	81	141
G. E.	1 yr. 1 mo.	Untreated between 5 and 8 mo. of age; treated between 8 mo. and 1 yr. of age	51.5	42	91	155	30	45.5	....	38	....	85	36	14	78	93.5	....	....	....	....	.....	91	152
Control	3 yr.	.....	58.7	48.8	103	174	37	58.5	84.5	50.5	52.5	..	40.6	16	79.7	84.7	72.8	22.2	71.7	97.5	116.9	87.2	144.5
J. D.	3 yr.	Began at 6 mo. of age	59	49	103	158.5	37	56.5	82	50	....	94.5	....	17.5	81.5	85.5	....	....	....	....	.....	84	144
C. D.	3 yr.	Began at 3 yr. of age	52	42.5	92	157	26.5	41.5	....	33.5	....	88	....	7	76	86.5	....	....	....	....	.....	....	151.5
Control	8 yr.	.....	63.5	56.3	114	182	44.3	69	98.5	60.2	61.2	..	45*	19.5	81.9	85	74.8*	20.2	69.2	99.2*	114.2*	86.7	143.7
M. B.	10 yr. 9 mo.	Began at 11 mo. of age and continued until 7 yr. old then discontinued for 1 yr.; continues since 8 yr. old	61.5	53.5	110	186	45.5	69	101	57.5	63	101	42.5	21	81	83	77	20	65	96	122.5	88	146
M. Y.	10 yr. 8 mo.	Began when 10 yr. 8 mo. old	59	49	102.5	168	36	58.5	....	53	....	102	45	12.5	85	94	....	22	....	....	.....	83	145
Control	8 yr.	.....	63.5	56.3	114	182	44.3	69	98.5	60.2	61.2	...	45*	19.5	89	85	74.8*	21.2	69.2	99.2*	114.2*	86.7	143.7
J. C.	11 yr. 11 mo.	Irregular to the age of 7 yr.; regular since	62	57.0	114	191	40	66	95	56.5	65	113	..	12	93	94.5	84	17.0	64	86	126	83	146.5
M. B.	12 yr. 3 mo.	Began at 12 yr. 3 mo. of age	64	52	112.5	173.5	40	62.5	....	57	....	106.5	46	15	88	86.5	....	16.5	....	....	.....	88	148
Control	8 yr.	.....	63.5	56.3	114	182	44.3	69	98.5	60.2	61.2	...	45*	19.5	81.9	85	74.8*	21.2	69.2	99.2*	114.2*	86.7	143.7
T. I.	13 yr. 2 mo.	Began at age of 8 yr.; regular since	64	58	116.5	181	44	72	100	60	68.5	112	48	17.5	85	89.5	77	18.5	73.5	98	111.5	85	146
M. H.	13 yr. 3 mo.	Began at 12 yr. of age	61	54	107	171	34	53.5	...	49	....	100	..	14	92.5	87	....	....	....	....	.....	....	138
Control	8 yr.	.....	63.5	56.3	114	182	44.3	69	98.5	60.2	61.2	...	45*	19.5	81.9	85	74.8*	21.2	69.2	99.2*	114.2*	86.7	143.7
T. I.	13 yr. 2 mo.	Began at 8 yr. of age; regular since	64	58	116.5	181	44	72	100	60	68.5	112	48	17.5	85	89.5	77	18.5	73.5	98	111.5	85	146
E. S.	13 yr. 4 mo.	Began at 13 yr. 4 mo. of age	59	50	99	174	34	53	....	....	....	93.5	43.5	13	82	86	....	16	....	....	.....	88.5	143
Control	8 yr.	.....	63.5	56.3	114	182	44.3	69	98.5	60.2	61.2	....	45*	19.5	81.9	85	74.8*	21.2	69.2	99.2*	114.2*	86.7	143.7
A. B.	19 yr. 8 mo.	Irregular between the ages of 2 and 8 yr.; none between ages of 8 and 11 yr.; regular since	67	59	123	208	52	82	....	....	69	122.5	55	24	83	84.5	....	....	....	108	.....	80.5	156
F. D.	23 yr.	Began at age of 23 yr.	63	47.5	108	183	39.5	65	94.5	49	52.5	105.5	47	13.5	83.5	86	68	21.5	66	97	128.5	81.8	156

* Indicates value for 7 year old control.

but this method has limitations, as was pointed out by Todd [17] and Köhler,[18] which led to Sontag's work of measuring all of the joints of the left upper and lower extremity in appraising skeletal growth.[19]

The stages of the eruption, primarily, and of the formation of teeth were established in order to obtain some basis for comparison of dentition in cases of treated and of untreated hypothyroidism. The stages are as follows: (1) calcification of crown, (2) beginning formation of root in crypt, (3) "migration" of crypt to midjaw, (4) presence of tooth at alveolar border and (5) occlusion.

RESULTS

A comparison of data for treated patients with hypothyroidism and data for recently treated or untreated patients of approximately the same age yields some striking results. The developmental differences brought out in seven such comparisons are given in the tables and figures.

G. E. and D. V.—Patient G. E., a girl aged 1 year 1 month, was treated between the ages of 5 and 8 months and was untreated from the age of 8 months until she was 1 year old. D. V., a boy 1 year 3 months of age, was treated from the age of 3 months on. Data for these 2 patients are given in the tables, and tracings of their roentgenograms are reproduced in figure 2. Study of this figure indicates that the faces of the 2 patients have approximately the same developmental status. There is some suggestion that G. E. has retarded mandibular development. The outstanding difference is in the cranial development, for there is a lag in the development of G. E.'s occipital and parietal areas. The frontal areas, however, superpose. The dimensions for the posterior part of the cranial base and the length of the skull for the 2 patients are given in table 1. The sutures of the vault and the cranial base are wide open, which is characteristic of the age. However, the spheno-occipital synchondrosis of G. E. is atypically wide. Note that there is no marked difference in the patterns of the 2 patients.

The data in table 1 indicate that the treated child (D. V.) has attained almost normal development. Some differences exist in the angular measurements, but these may be within the range of variability or of type.

The dental development in both cases is at normal levels. There is some evidence of retardation in carpal development in D. V., for there are no carpal centers of ossification in his roentgenogram. The roentgenograms of G. E.'s wrists indicate normal development.

J. D. and C. D.—Patient J. D., a 3 year old boy, received thyroid therapy from the age of 6 months. C. D., a 3 year old girl, was not

17. Todd, T. W.: Atlas of Skeletal Maturation, St. Louis, C. V. Mosby Company, 1937.

18. Köhler, A.: Roentgenology, translated from the fifth German edition by A. Turnbull, New York, William Wood & Company, 1928.

19. Sontag, L. W.: Rate of Appearance of Ossification Centers from Birth to the Age of Five Years, Am. J. Dis. Child. **58**:949 (Nov.) 1939.

treated. Data for these 2 patients are given in the tables, and tracings of their roentgenograms are reproduced in figure 3. Examination of this figure indicates that the untreated child has marked retardation in the development of the facial area. Note the 10.5 mm. difference between the

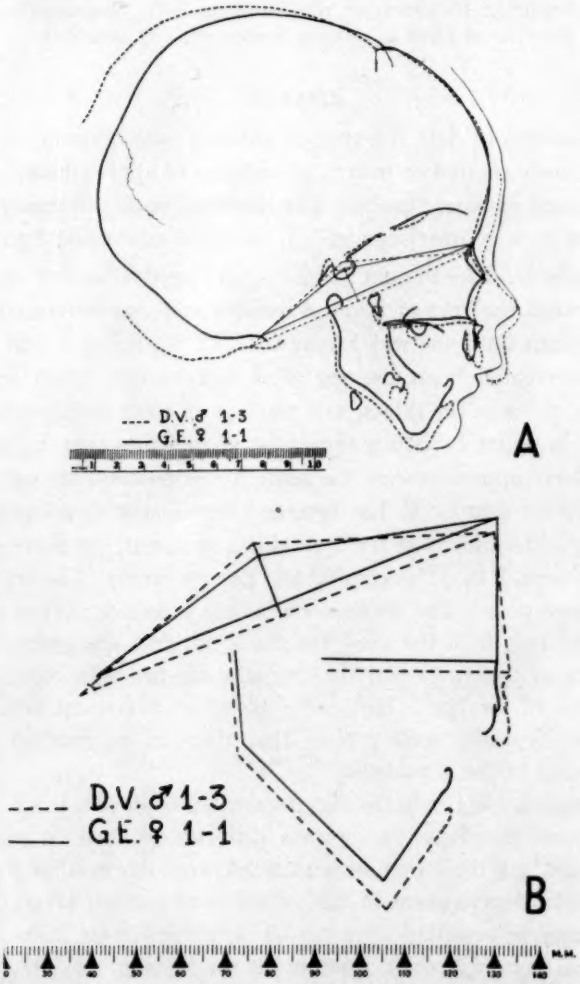

Fig. 2.—*A*, superposed tracings of the lateral roentgenograms of D. V., a treated cretin, and G. E., an irregularly treated cretin. The scale indicates the degree of photographic reduction. A description of this and subsequent illustrations will be found in the text. *B*, composite representation of *A*.

measurements for the respiratory area (*N-NS*) for the 2 patients, the 16 mm. difference in the height of the upper part of the face (*N-I*), the 16.5 mm. difference in the mandibular lengths (*GO-GN*) and the

dwarfing of the nasal bone (table 2). Though C. D.'s mouth was open when the roentgenogram was made and consequently measurement of the total height of the face was impossible, it is evident from the tracing that this dimension for C. D. was far smaller than that for the treated

TABLE 2.—*Character of Cranial Sutures of Thirteen Persons with Hypothyroidism**

Patient	Occipito-Parietal	Fronto-Parietal	Spheno-occipital
D. V.	W-N	W-N	—
G. E.	W-N	W-N	W
J. D.	N	N	—
C. D.	W	W	W
M. B.	N	N	N
M. Y.	W	W	—
J. C.	N	N	N
M. B.	W	W	—
T. I.	N	N	N
M. H.	N	W	W
E. S.	W	W	W
A. B.	N	N	W
F. D.	W	W	W

* W signifies that the suture was wide; N, that suture was normal; W-N, that it was wide but characteristic for the age, and —, that it was not clearly defined in the roentgenograms.

TABLE 3.—*Dental Development and Carpal Ossification Patterns*

		Tooth Development								
Patient	Age	Central	Lateral	Cuspid	First Bicuspid	Second Bicuspid	First Molar	Second Molar	Third Molar	Carpal Ossification
D. V.	1 yr. 3 mo.	V*	V	IV	IV	III	1	..	..	No carpals
G. E.	1 yr. 1 mo.	V	V	IV	IV	III	1	..	..	Normal
J. D.	3 yr.	V	V	V	V	V	2+	..	..	Normal
C. D.	3 yr.	IV	IV	IV	IV	IV	2	..	..	Delayed
M. B.	10 yr. 9 mo.	5	5	5	4	4	5	4	1	Normal
M. Y.	10 yr. 8 mo.	4	4	3	4	4	4+	..	..	3 carpals
J. C.	11 yr. 11 mo.	5	5	3+	3	3	5	3	..	Normal
M. B.	12 yr. 3 mo.	5	5	3+	3+	3+	5	3	..	4 carpals
T. I.	13 yr. 2 mo.	5	5	5	5	5	5	5	2	Normal
M. H.	13 yr. 3 mo.	5	5	3	3+	3+	5	2	..	Approximately 8 yr.
T. I.	13 yr. 2 mo.	5	5	5	5	5	5	5	2	Normal
E. S.	13 yr. 4 mo.	5	5	3+	3+	4	5	3	..	3 yr.
A. B.	19 yr. 8 mo.	5	5	5	5	5	5	5	Absent	Normal
F. D.	23 yr.	5	5	3+	4	4	4	3	3	6 carpals

* Roman numerals indicate deciduous teeth.

child. The point *GO*, the mandibular angle, has failed to move downward and backward. Forward movement of the face also lags, as is partially indicated by comparison of the lengths of *B-NS*. The brain case is underdeveloped, particularly in the occipital and parietal areas. There is an 11 mm. difference between the lengths of the cranial bases of the 2 children. The sutures of the vault and the spheno-occipital synchondrosis

of the untreated cretin are abnormally wide. The craniofacial patterns, however, are essentially alike.

The facial development of J. D., the treated patient, is at a normal level, with a definite retardation of 15.5 mm. in the cranial length, which tends to obscure the impeded development in the untreated patient.

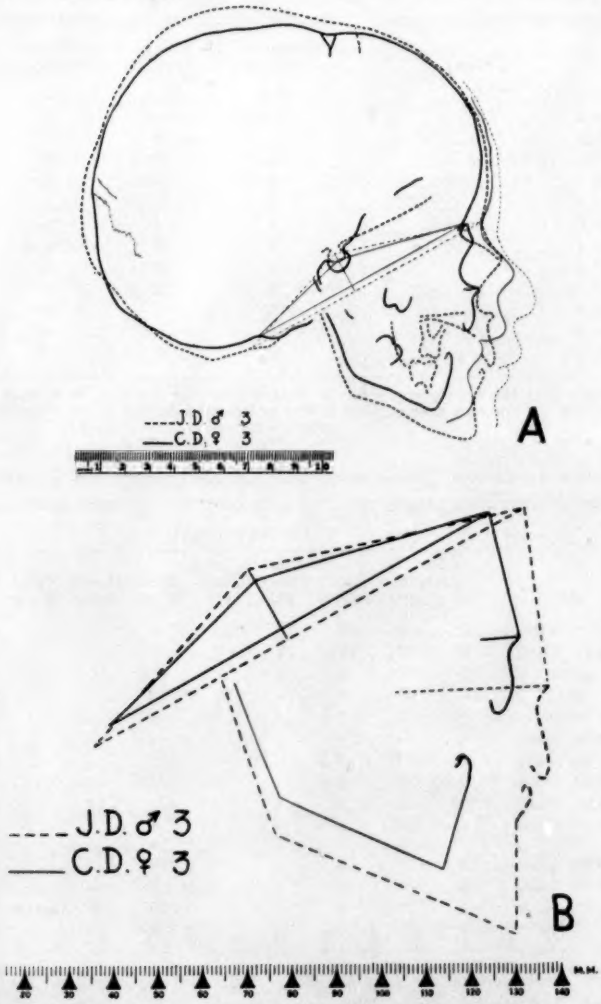

Fig. 3.—*A*, superposed tracings of the lateral roentgenograms of J. D., a treated cretin, and C. D., an untreated cretin. *B*, composite representations of *A*.

C. D. is far behind in dental development. No teeth are present in the oral cavity, and carpal ossification is also delayed. J. D. shows normal eruption and formation of teeth, with a wrist development characteristic of the age.

M. B. and M. Y.—M. B., a 10 year 9 month old girl, was treated from the age of 11 months to the age of 7 years, when treatment was discontinued for a year, then resumed and continued. M. Y., a girl 10

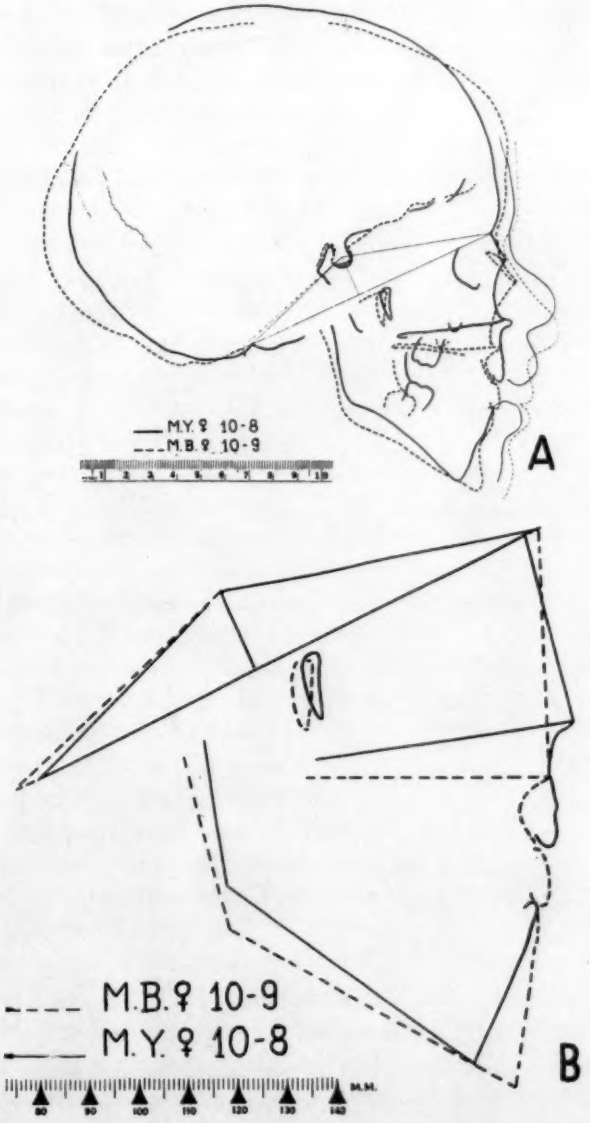

Fig. 4.—*A*, superposed tracings of the lateral roentgenograms of M. B., a treated cretin, and M. Y., an untreated cretin. *B*, composite representation of *A*.

years 8 months of age, was not treated. Data for these 2 patients are given in the tables, and tracings of their roentgenograms are reproduced in figure 4. Examination of this figure shows that there are outstand-

ing differences in the development of the facial area. The height of the upper part of M. Y's face is below normal, and if one mentally corrects the mandibular position of M. Y. striking differences between the total heights of the faces are also revealed. Differences in cranial development

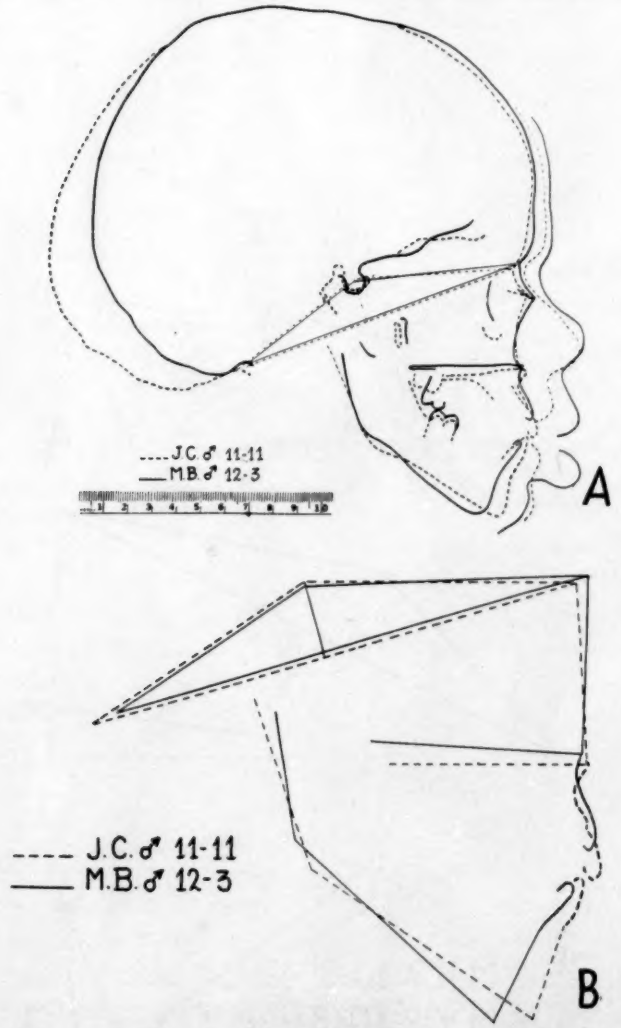

Fig. 5.—*A*, superposed tracings of the lateral roentgenograms of J. C., a treated cretin, and M. B., an untreated cretin. *B*, composite representation of *A*.

are also present, in the frontal and occipital regions. The difference in the lengths of the skulls is 16 mm. M. Y's cranial base is shorter by 7.5 mm. The height of the skull of the untreated patient, however, is the greater. There is some difference in angular measurements, but their

significance is at present obscure. The cranial sutures of the child with retarded development are infantile in type.

Comparison with the 8 year old control further emphasizes M. Y.'s retardation in growth. The treated child shows indications of slight retardation in the development of the face, with more definite evidence of slowed growth in the cranial base. The angular values are approximately the same as those of the normal except *S-GO-GN,* which is 122.5 degrees in the roentgenogram of the treated cretin and 114.2 degrees in that of the 8 year old control (table 2).

Dentition in the untreated child is generally retarded, and there are but three carpal centers of ossification visible in the roentgenogram of the wrist. The dental and carpal development of M. B. are normal.

J. C. and M. B.—The treatment of J. C., a boy aged 11 years 11 months, was irregular to the age of 7 years but has been regular since. M. B., a boy aged 12 years 3 months, had not been treated. He was the only patient in the series who had a large palpable mass in the neck. Data for these patients are given in the tables, and tracings of their roentgenograms are reproduced in figure 5. Examination of this figure shows that facial growth is at approximately the same level in both patients, though *B-NS* is 6.5 mm. shorter in M. B.'s roentgenogram. Differences, however, are apparent in the cranial development; M. B.'s lack of occipital and posterior parietal expansion may be noted. The difference in the lengths of the skulls is 17.5 mm., while the cranial base of M. B. is but 2.5 mm. shorter than that of J. C., the treated patient. The sutures of the vault of the thyroid-deficient child are wide open. Comparison with the 8 year old control shows that the facial areas of both the treated and the untreated patient have suffered. However, the cranial growth of J. C., the treated patient, is, on the basis of interpolation, probably up to the normal level.

The dental patterns of both children are approximately comparable and exhibit some slight delay in the eruption of the canines, the premolars and the second molars. However, a difference in the appearance of the carpal centers of ossification is noted; J. C. exhibits the number typical for the age, while M. B. shows but four centers.

T. I. and M. H.—T. I., a girl aged 13 years 2 months, had been treated since the age of 8 years. M. H., a girl aged 13 years 3 months, had been treated since the age of 12 years. Data for these patients are given in the tables, and tracings of their roentgenograms are reproduced in figure 6. Study of this figure indicates that there is a pronounced lag in the facial development of M. H. The occipital and parietal bones and the posterior two thirds of the frontal bones have also been affected. The cranial base is shortened by 9.5 mm. The frontoparietal and sphenoccipital sutures are atypically wide. T. I., the better treated child, shows

development which comparison with that of the 8 year old control suggests is normal or near normal. M. H. shows a degree of development which is comparable to that typical of a chronologic age under 8 years.

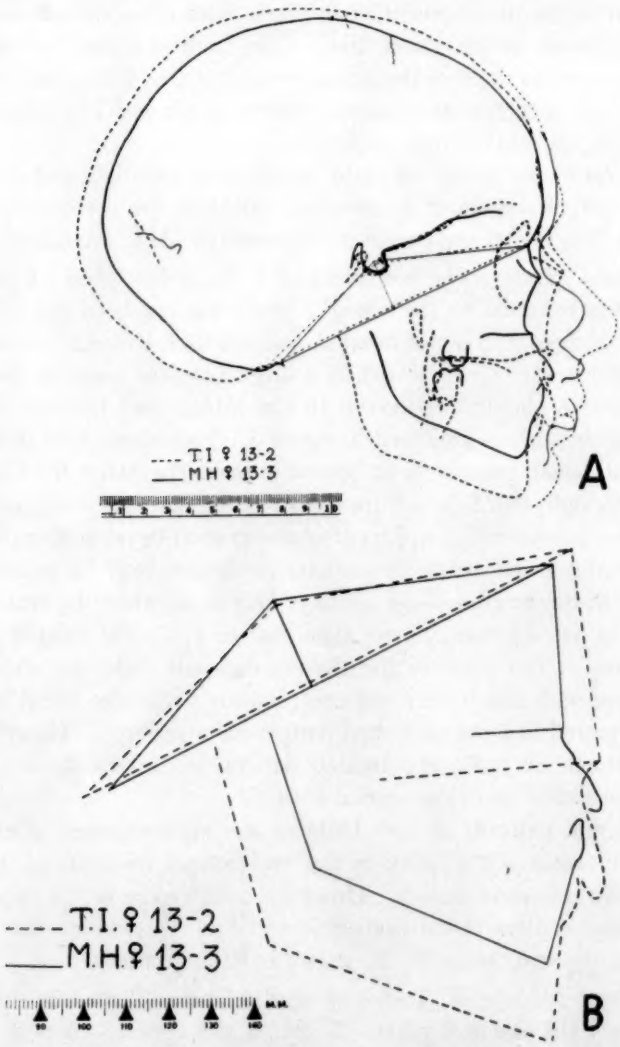

Fig. 6.—*A*, superposed tracing of the lateral roentgenograms of T. I., a treated thyroid-deficient child, and M. H., a recently treated cretin. *B*, composite representation of *A*.

The retardation of development is generalized, particularly in the facial area.

Eruption of M. H.'s canines, bicuspids and second molars is retarded, while T. I. shows good dental development. M. H.'s carpal ossification

is at the 8 year level, and that of the child with the more adequate therapy is normal.

T. I and E. S.—Data for T. I. are given in the preceding section. E. S., a girl aged 13 years 4 months, had been untreated, except for a

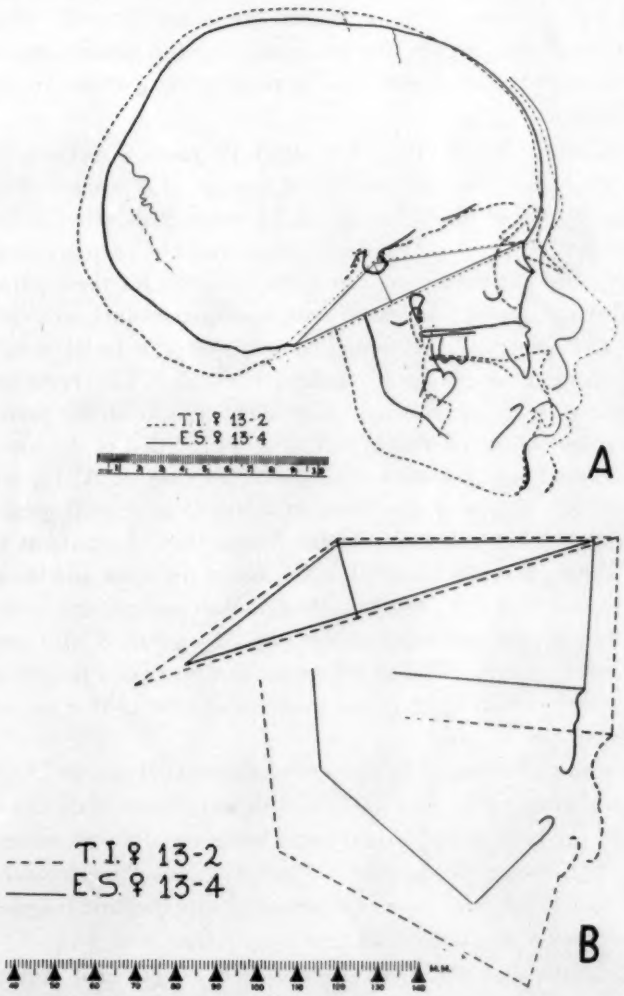

Fig. 7.—*A*, superposed tracings of the lateral roentgenograms of T. I., a treated thyroid-deficient child, and E. S., an untreated cretin. *B*, composite representation of *A*.

short period at the age of 3 or 4 years. Data for these patients are given in the tables, and tracings of their roentgenograms are reproduced in figure 7. Study of this figure indicates that E. S. has a generalized retardation in facial development of a striking degree. Disturbed growth

is also reflected in the posterior and middle portions of the cranium and in the cranial base. This patient has not attained the level of development of the 8 year old control. The sutures of the vault and the base exhibit infantile characteristics. A generalized deceleration of craniofacial growth is indicated.

The dental and carpal development of T. I. were reported on in the foregoing section; those of the untreated cretin are delayed. Formation and eruption of the cuspids, the bicuspids and the molars are delayed, and the roentgenogram of the wrist is roughly comparable to that of a 3 year old child.

A. B. and F. D.—A. B., a boy aged 19 years 9 months, received irregular treatment from the age of 2 to the age of 8 years and no treatment from that time until the age of 11 years 9 months; it has been regular since. F. D.,[20] a 23 year old man, has not been treated except for a short period at the age of 3 or 4 years. Data for these patients are given in the tables, and tracings of their roentgenograms are reproduced in figure 8. Study of this figure shows that the facial area of the untreated patient is markedly underdeveloped. The retardation of development is again generalized. The development of the parietal and occipital regions of the untreated patient is behind that of the control. It must be pointed out, however, that the brain case of A. B., who was treated, shows a degree of development which is somewhat greater than that usually attained by adults; so the comparison of craniums must be tempered by this consideration. The sutures of the vault and the spheno-occipital region of F. D., the thyroid-deficient patient, are wide. The spheno-occipital synchondrosis of the treated control is also somewhat wider than that usually noted at this age. The untreated patient shows a degree of development which is not comparable even to that normal for a chronologic age of 8 years.

The dental and carpal development of the treated patient, A. B., give evidence of maturity. F. D.'s pattern of dental growth indicates marked retardation, the central and lateral teeth being the only permanent teeth erupted. The roentgenogram of the wrist shows the presence of six centers of ossification and there is evidence of stippling and fragmentation in the epiphyses of the knee joint.

These results may be briefly summarized. Untreated cretins show retardation in the growth of the cranium and the face. Facial heights, *N-NS, N-1* and *N-GN,* and facial length, *B-NS,* lag behind those of treated controls. The face fails to move downward and forward, and the gonial point lags in its downward and backward course. Individual

20. It is of interest that the younger brother of F. D., who is now 13 years old, is also an untreated cretin and exhibits a similar retardation in craniofacial and general growth.

bones, such as the mandible, the maxilla and the nasal bone, are also profoundly affected in their dimensional increases. Cranial expansion, practically in the occipital and parietal areas, is retarded; the frontal

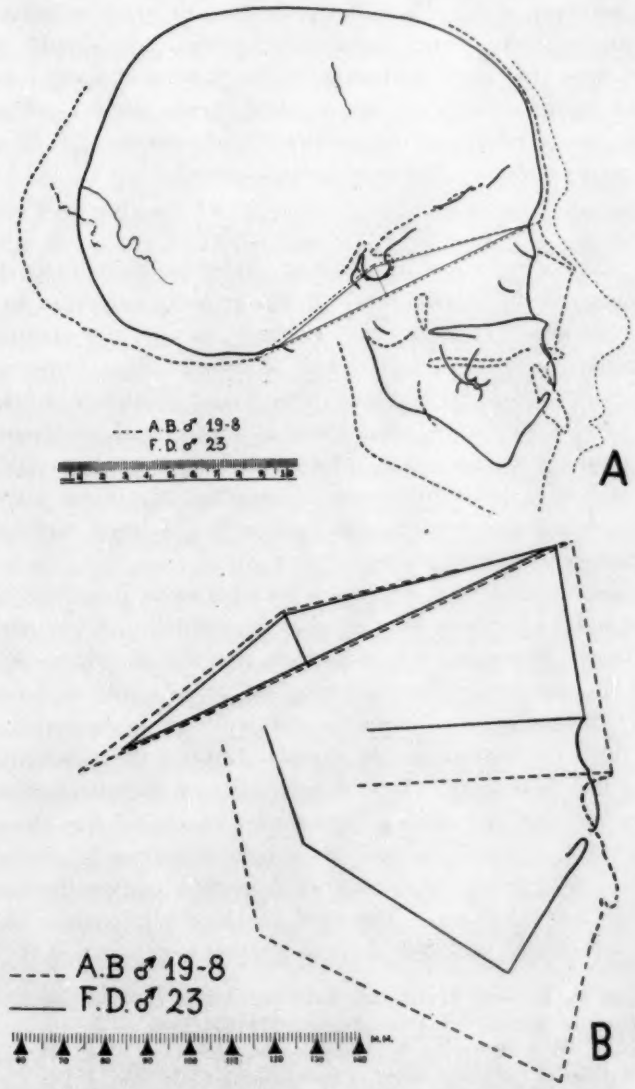

Fig. 8.—*A*, superposed tracings of the lateral roentgenograms of A. B., a treated cretin, and F. D., an untreated cretin. *B*, composite representation of *A*.

area, however, does not appear to differ much from that of the treated controls. The cranial base formed by the squamous portion of the occipital bone, the sphenoid bone and the cribriform plate of the ethmoid

bone, does not attain normal development. The developmental directions or patterns in treated and untreated patients do not differ essentially. There is some evidence that even the treated cretin may not attain normal levels of craniofacial growth, but the response is favorable. In addition, it is evident that patients with hypothyroidism have delayed sutural, dental and carpal development. It should also be mentioned here that no disturbances in the pattern of tooth formation were noted in the roentgenograms of the patients studied. This does not negate the possibility of a slowed rate of formation, such as was reported for monkeys by Ziskin and Applebaum.[21]

COMMENT

The studies of the Brush Foundation, under the direction of Todd,[22] have emphasized the susceptibility of the growing organism to metabolic disturbances. Todd has also pointed out that the cranium and face, particularly, possess a high degree of vulnerability. Other investigators, notably Schour, Brodie and King[23] and Mortimer, Levine and Rowe,[24] have demonstrated that there is craniofacial involvement in cases of pituitary dysfunction. This investigation presents additional evidence of both a quantitative and a qualitative nature for associating a specific uniglandular endocrinopathy, thyroid deficiency, with retardation in craniofacial development.

We believe that thyroid deficiency does not exert its effects because of a topographic specificity or a peculiar susceptibility of any particular bone or bones. Moreover, it is not certain that the disturbance is pathognomonic of cretinism. The thyroid gland plays a role in the control of cellular metabolism. Absence or deficiency of its secretion exerts adverse effects on those processes, possibly through decreased nutrition. Silberberg and Silberberg,[25] from their studies on the effect of thyroidectomy on cartilage and bone in guinea pigs, concluded that the growth of cartilage and probably the growth of bone are directly affected, and they implied that this occurs primarily through a nonspecific metabolic influence of thyroidectomy. The level of blood phosphatase has been related to osteoblastic activity. It is of interest to report that F. D. had

21. Ziskin, D. E., and Applebaum, E.: The Effect of Thyroidectomy upon Growing Teeth of Monkeys, J. Dent. Research **19**:304, 1940.

22. Todd, T. W.: Assessing the Hazards of Childhood, J. Med. **12**:426, 1931; Objective Ratings of the Constitution of the Growing Child, Am. J. Dis. Child. **55**: 149 (Jan.) 1938; Facial Growth as an Objective Record of Child Health, Angle Orthodontist **9**:20, 1939; footnote 17.

23. Schour, I.; Brodie, A. G., and King, E. Q.: The Hypophysis and the Teeth, Angle Orthodontist **4**:285, 1934.

24. Mortimer, H.; Levine, G., and Rowe, A.: Cranial Dysplasias of Pituitary Origin, Radiology **29**:135, 1937.

25. Silberberg, M., and Silberberg, R.: Effect of Thyroidectomy on Cartilage and Bone, Am. J. Path. **16**:505, 1940.

the low level of 3 Bodansky units of phosphatase per hundred cubic centimeters of blood, as compared to the normal level of about 8 units.

The retardation in growth is generalized in the cranium and (or) face. However, it is likely that a chronologic specificity exists; that is, that the site of delayed growth is determined by the metabolic gradient at the time of disturbance. The greater the activity of a tissue the greater its vulnerability. It is for this reason that the fetal and immediate postnatal periods are so significant in craniofacial development.

There is good evidence which indicates that the glandular deficiency which leads to the symptoms of clinical hypothyroidism may have its inception during the most critical period of growth, that is, the fetal period. Normally, the center for the distal epiphysis of the femur may be detected roentgenographically at birth. It has been shown that this center is not present in very young patients with hypothyroidism. Such an absence was noted in 1 patient of our series not reported on here. This might indicate that the differentiating effect of the thyroid was lacking in the prenatal period. It has been pointed out that many of the growth processes are functioning at maximum velocity during this period; therefore, it is not surprising that our results demonstrate the susceptibility of the craniofacial area to disturbance in development. In embryonic development the thyroid is one of the first organs to be differentiated, being distinguishable at about the third week. This fact alone suggests its fundamental importance in growth. Studies on the physiologic activity of the fetal gland do exist. By some it is maintained that the fetal thyroid is inactive during embryonic life in lower animals and that the placenta is not permeable to maternal thyroid hormone. On the other hand, the tadpole test has demonstrated the presence of small amounts of hormone in the fetal thyroid.[26] Engelbach [7a] has expressed the belief that there is little evidence of thyroid activity before birth. Dorff,[27] on the other hand, cited the occurrence of cretinism in one of heterozygous twins as demonstrating that the fetal thyroid was a functional unit and that the maternal gland did not influence the state of the fetus enough to prevent cretinism.

The following portion of the discussion is concerned with a consideration of the growth response in the cranium, the face and the teeth in treated and untreated hypothyroidism.

The response in the cranium is rather typical. There appears to be a gradient of retardation; the occipital area suffers most severely, the parietal area next and the frontal area least. This difference is susceptibility to disturbance in development may be an expression of the growth

26. Aldrich, C. A.: The Endrocine Glands and Growth: The Thyroid, J. Pediat. **8**:380, 1936.

27. Dorff, G. B.: Sporadic Cretinism in One of Twins, Am. J. Dis. Child. **48**:1316 (Dec.) 1934.

tendencies inherent in these regions and may indicate a growth or incremental gradient from the occipital to the frontal region.

The failure in cranial expansion may be attributed to the reduction of osteoblastic activity on the external and the internal osseous surfaces and at the sutural surfaces, which appeared abnormal roentgenographically.

The shortening of the cranial base is probably explicable on the basis of diminished chondral activity at the sphenoethmoid and spheno-occipital synchondroses. The latter was shown to be irregular and wider than normal, changes indicative of a disturbance in the epiphysis. (Chondro-epiphysitis and stippling have been reported by Benjamin and Miller,[28] Reilly and Smyth [29] and Schaefer, Strickroot and Purcell [30] to occur in other epiphyses in hypothyroidism.) Delayed union after experimental thyroidectomy was reported by Liddell [9] and by Todd, Wharton and Todd.[11] Engelbach [7a] and Wolf [8] also called attention to the persistence of open fontanels in cretins, a symptom of retardation in maturation. These observations parallel the signs of delayed maturation elsewhere in the skeleton, for example, the absence or delay in appearance of the centers of ossification and the retardation of epiphysial maturation and closure.

Retardation in anteroposterior facial growth is induced by the lag in the development of the cranial base, which normally carries the upper part of the face forward through its hafting to the anterior portion of the base. The mandibular ramus normally goes backward because of its association with the posteriorly descending temporal bone. Both of these processes suffer in the cretin. The evidence indicates that the dysplasia within the facial area itself is generalized rather than localized. Thus, though individual bones, such as the mandible, the nasal bone and the maxilla, suffer in their incremental gain, the velocity of growth is slowed generally. Brodie [16] has shown that the developmental trends in the craniofacial patterns of children from the age of 3 months to the age of 8 years follow a straight, apparently predetermined or inherent course. Similarly, the development of the cretin child appears to follow in the direction of the development of the normal child, which suggests conformity to pattern but at a slowed rate. Further confirmatory evidence, however, is necessary. The growth reaction in the face again is attributed to lowered osteoblastic activity.

The modification in soft tissue profile which is reported in cretins is at least partly due to the disturbance in skeletal growth. As Wolf [8] has pointed out, the depressed nasal bridge results from the failure of growth

28. Benjamin, B., and Miller, P. R.: Hypothyroidism as a Cause of Disease of the Hip, Am. J. Dis. Child. **55**:1189 (June) 1938.

29. Reilly, W. A., and Smyth, F. S.: Stippled Epiphyses with Congenital Hypothyroidism, Am. J. Roentgenol. **40**:675, 1938.

30. Schaefer, R. L.; Strickroot, F. L., and Purcell, F. H.: Endocrine Implications of Juvenile Character—Epiphysitis, J. A. M. A. **112**:1917 (May 13) 1939.

in the cranial base, and the consequent failure of the face to move forward is reflected at the nasion. The dwarfed nasal bone is also responsible for the concave appearance of the nose. The delay in the dental eruption pattern reported for 6 of the untreated and for 1 of the treated patients is not a new observation and is a further reflection of retarded development.

Ziskin and his co-workers [31] have reported that there is a slowed rate of dentin formation in thyroidectomized rats and monkeys. Roentgenographic assessment of tooth formation was attempted in our study, but it cannot be considered as accurate a method as histologic examination. Some retardation was suggested by the wide apical foramens of many of the untreated patients. There was no evidence, however, of a small tooth size. Further investigation of this problem is necessary.

The histopathologic basis of the osseous and chondral changes in hypothyroidism has been investigated. An abnormal layer of bone, called *Querbalken* has been observed at the epiphysial-diaphysial junction. This is ascribed to a diminution in the activity of the marrow, resulting from thyroid hypofunction. Observations on a 10 year old male cretin revealed that ossification of the capital epiphysis of the femur had not yet begun but that the altered cartilage offered clear evidence of perversions of orderly bone development. In some places the cartilage had apparently disintegrated and been replaced by cystic areas filled with a dark-staining fluid. Looser,[32] in anatomic observations, noted diffuse and irregular ossification of the capital epiphysis, with incomplete replacement of the cartilage by bone. Liquefaction of the cartilage and fibrotic changes in it are responsible for the formation of fissures in the epiphyses followed by fragmentation of portions of the head with liberation of the joint bodies. Silberberg and Silberberg [25] studied the changes in thyroidectomized guinea pigs. They reported that there were accelerated sclerosis of the cartilage matrix, failure of the epiphysial cartilage to undergo regular and full hypertrophy and incomplete and delayed ossification of abnormal cartilage.

It has been shown that both dental and ossification patterns respond rapidly to treatment.[33] This is confirmed by the normal development of dentition and ossification in most of our treated patients and is suggestive of some similarity in mechanism in eruption and ossification, which are both differentiative processes.

The difference in the craniofacial, dental and ossification patterns which were demonstrated in the series presented not only shows the

31. Ziskin, Salmon and Applebaum.[18] Ziskin and Applebaum.[21]

32. Looser, E.: Die Kretinenhüfte, Schweiz. med. Wchnschr. **59**:1258, 1929.

33. Wilkins, L.: Rates of Growth, Osseous Development and Mental Development in Cretins, J. Pediat. **12**:429, 1938. Bronstein, I. P.: Unpublished data. Benda.[6]

effects of a thyroid deficiency but demonstrates the efficacy of thyroid therapy in maintaining the developmental processes involved in the growth of these structures.

In those instances in which, for one reason or another, thyroid therapy is discontinued growth is arrested. It is not feasible to test this observation deliberately under experimentally controlled conditions. If this were possible it would be interesting to record the retardation in young and in older persons. One of our patients (G. E.) for whom a diagnosis of hypothyroidism was made at an early age (5 months) was untreated from the age of 8 months to the age of 1 year. This child presents evidence of retardation in growth of the craniofacial area in comparison with her control, D. V.

In general, the differences which existed between normal controls and treated cretins of the same age were not marked (except the measurements of the skull of J. D.). This leads one to conclude that when thyroid therapy is begun at an early age there is at least a possibility for good, though not necessarily optimal, development and that the degree of response may be related to the dosage as well as to Todd's constitutional "scarring."

SUMMARY AND CONCLUSIONS

Craniofacial, dental and carpal ossification patterns of development of untreated children with hypothyroidism lag behind those of children given thyroid therapy. The deficiency in the cranium lies in the occipital, the parietal and, to much lesser extent, the frontal area. The cranial base is shortened, and the spheno-occipital synchondrosis and the sutures of the vault are abnormally wide. The face shows a generalized retardation of growth as a result of the slowed velocity of growth of its components, that is, the mandible, the maxilla and the nasal bone. The teeth are delayed in their eruption, but they are not malformed. Differentiation and ossification of carpal centers are disturbed and retarded, and the roentgenograms show persistence of infantile characters.

Craniofacial, dental and carpal patterns of development in untreated children with hypothyroidism are retarded when compared to those of normal subjects of the same age. The differences are merely an accentuation of those noted between treated and untreated cretins.

Children with hypothyroidism who have been treated regularly since early childhood closely approach normal levels of craniofacial development. Their pattern of dental development and progress in ossification are normal.

Thyroid deficiency affects craniofacial growth by retarding its velocity rather than by modifying its pattern.

DEVELOPMENT OF THE PLANTAR RESPONSE IN HEALTHY INFANTS

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Since the appearance of the original article by Babinski,[1] in which the association of lesions of the pyramidal tract with hyperextension and abduction of the great toe was pointed out, the plantar response of infants has been the subject of extensive investigation and speculation. This interest was created by the observation that digital extension on plantar stimulation is common among newborn infants. No less than seventy articles in eight different languages have been published on the subject as it relates to infants specifically, and countless volumes have appeared on the pathognomonic aspects of the Babinski sign in adults—not to mention significant work with animals, particularly the primates. These studies have covered a great many details. The incidence of dorsiflexion and of plantar flexion of all the toes and of the great toe has been painstakingly calculated by a number of investigators. The extent and variability of the response and the character of the response under various conditions, that is, when the child is awake or asleep, wet or dry, and warm or cold, have received extensive study. The type of applicator, the area stimulated and the degree of pressure applied are considered significant. The literature on the subject has become so voluminous that several reviews have been published.[2] It is generally recognized that the plantar response of infants is labile and that variations in the response do not necessarily possess pathognomonic connotations.

The present study was undertaken for the purpose of determining the advancing specificity of the reaction as an expression of neural maturation. It is based on a study of 75 children, ranging in age from birth

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From the Normal Child Development Study of the Department of Pediatrics, Columbia University College of Physicians and Surgeons, and the Babies Hospital.

1. Babinski, J.: Sur le réflexe cutané plantaire dans certaines affections organiques du système nerveux central, Compt. rend. Soc. de biol. **48**:207-208, 1896.

2. Feldman, W. M.: The Nature of the Plantar Reflex in Early Life and the Causes of Its Variations, Am. J. Dis. Child. **23**:1-40, (Jan.) 1922. Richards, T. W., and Irwin, O. C.: Plantar Responses of Infants and Young Children: An Examination of the Literature and Reports of New Experiments, Studies in Child Welfare, Iowa City, University of Iowa, 1934, vol. 11, no. 1, p. 146. Waggoner, R. W., and Ferguson, W. G.: The Development of the Plantar Reflex in Children, Arch. Neurol. & Psychiat. **23**:619-633 (April) 1930.

to 5 years. Repeated examinations were made at monthly or longer intervals. Records of a total of 1,011 observations were made, of which 74 were on motion picture film and 937 were written protocols. The stimulus consisted of a light stroke with a toothpick along the lateral aspect of the sole and across the metatarsal arch to a point proximal to the great toe. Notes were made of the reactions observed, including

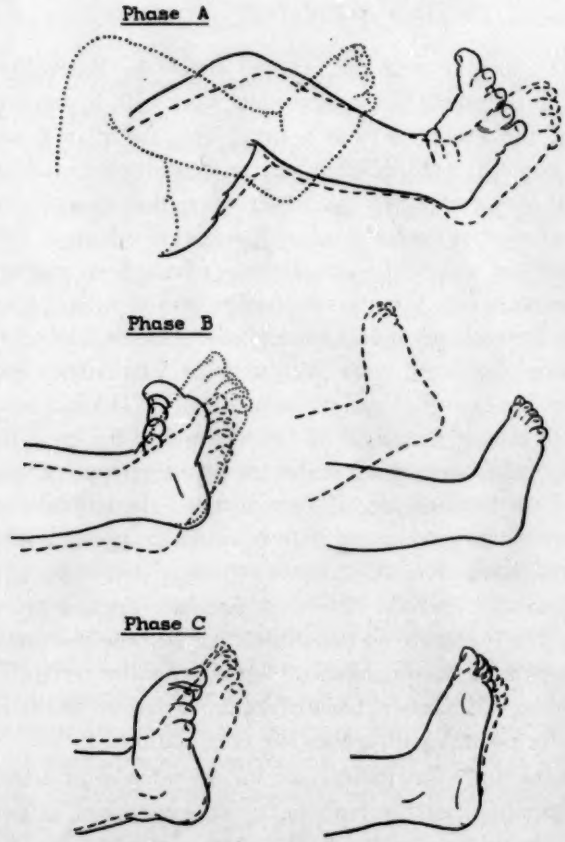

Fig. 1.—Line drawings made from successive frames of motion picture film. *Phase A*, the mass reflex phase characteristic of the newborn infant. The order of movement in the drawing is indicated thus: (1) the broken line, (2) the solid line and (3) the dotted line. *Phase B*, reactions characteristic of the transition phase. The order of movement in the drawing at the left is the same as in *A*, but in the drawing at the right it is indicated by (1) the solid line and (2) the broken line. *Phase C*, two types of response characteristic of the segmental reflex phase. The order of movement in the drawing at the left is indicated by (1) the broken line and (2) the solid line and in that at the right by (1) the solid line and (2) the broken line.

movements of the leg as well as flexion and extension of the toes. On examining the records it appeared that detectable developmental change

was expressed in (1) progressive restriction of the segments involved in the reaction and (2) a tendency toward plantar flexion as the child grew older. Accordingly the reactions observed have been allocated to three phases in which gross developmental changes in plantar response were revealed. Selection of the phases was based on the following considerations.

CRITERIA USED IN RATING THE PHASE OF DEVELOPMENT OF THE PLANTAR REFLEX

A. The Mass Reflex Phase:—The reaction of the newborn infant to plantar stimulation almost invariably involves movements of the entire leg, that is, contraction of the flexor muscles at the hip, knee and ankle

Number of Observations Made at Each Age Interval

Midpoint of Age Interval, Days	Number of Observations
20	133
60	93
100	72
140	58
180	60
220	63
260	59
300	44
340	46
380	38
500	143
700	84
900	36
1,100	39
1,300	16
1,500	14
1,700	13

joints as well as dorsiflexion of the toes. Sudden withdrawal of the extremity is the most consistent aspect of the response. It is usually accompanied by dorsiflexion of all the toes, by fanning or by dorsiflexion of the toes followed by plantar flexion. But it is the sudden, total reaction of the entire extremity which is most obvious. Line drawings in *A* of figure 1 illustrate this phase of the response.

B. The Transition Phase.—Within a few months it is observed that the speed of the withdrawal response is diminished and that fewer segments may be involved. Also, the withdrawal may consist principally of an abductor response of the leg rather than of immediate flexion on the abdomen. Plantar flexion of the digits is more common, especially as an initial move, though during this time there may be variation in the movements of the toes and the great toe. Whenever the response was not clearly defined either as a mass reflex or as a segmental response, a positive rating was accredited to the transition phase. When the response

was restricted to the foot segment but extension of the digits was marked, plus ratings were assigned to both the transitional and the segmental phase. In *B* of figure 1 reactions characteristic of the transition phase are illustrated.

C. The Segmental Reflex Phase:—With advancement in neural maturation, the response to plantar stimulation becomes progressively restricted until it consists primarily of movements of the ankle and toes. Ankle movements are flexion, inversion and eversion, and the common response of the digits is plantar flexion. At the beginning of this phase digital flexion is frequently carried out by the metatarsal joints, though later it is more likely to be limited to the distal phalanges. The move-

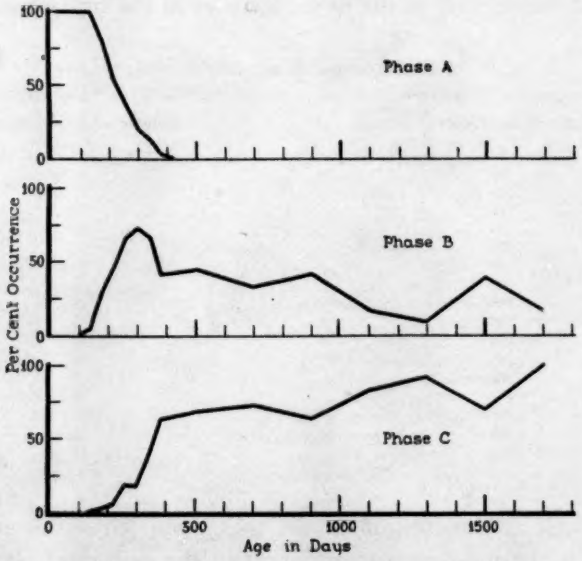

Fig. 2.—Curves indicating the percentage occurrence of each phase of the development of the plantar response during various age intervals.

ments are much slower than those characteristic of the mass reflex. If there is a withdrawal movement it is deliberate, usually abduction of the hip, which is often accompanied by such a remark as "It tickles." Sometimes the older children show only slight movements in the toes or even no detectable response. Characteristic features of this phase are illustrated by the line drawings in *C* of figure 1.

ANALYSIS OF THE DATA

After the observations were allocated to one of the phases of development, according to the foregoing criteria, it was possible to calculate the incidence of each phase within any desired age interval. The intervals

selected were forty days during the first year and two hundred days thereafter. The number of observations made at each age interval is shown in the table. The incidence of each phase during the various age intervals is shown in figure 2. The distribution curves in figure 3 show

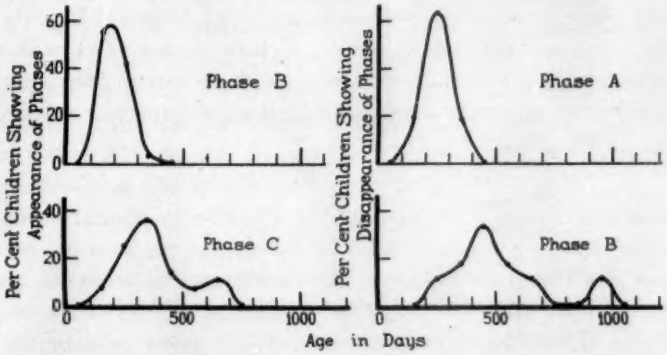

Fig. 3.—Distribution curves showing the percentage of children manifesting the appearance and the disappearance of each phase at various age intervals.

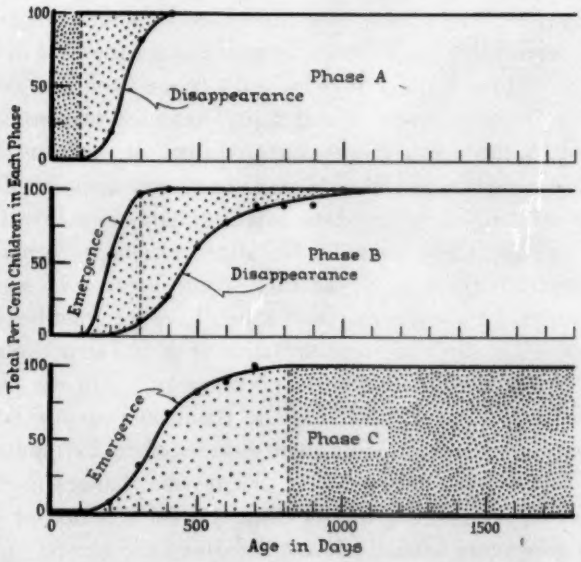

Fig. 4.—Ogives showing the total percentage of children who had exhibited the appearance and the disappearance of each phase at any time.

the age period at which the onset and the disappearance of each phase most commonly occurred. The ogives in figure 4 show the total percentage of children in whom a phase had been exhibited or had disappeared at any given age. The shaded areas between the ogives indicate

the percentage manifesting a phase at any given time. Thus it is seen that the mass reflex was common to all children in the group during the first one hundred days of life and that by the end of two and one-half years the segmental reflex had appeared in all the children. However, because of individual variations in the exhibition of dorsiflexion of the toes, some positive ratings for phase B have been recorded for this time. Undoubtedly, a more intensive study of this phenomenon will reveal details which would justify the division of development into additional phases and would more adequately differentiate the transitional from the segmental reflex phase.

COMMENT

It seems evident that the changes in response to plantar stimulation reflect reorganization or maturation of the neural mechanisms involved. It appears that the gross aspects of the developmental sequence are contained in an appraisal of the mass and segmental aspects of the response as well as in minute distinctions between digital flexor or extensor reactions. There was some indication that the onset of the segmental phase occurs about the time that cortical participation is evident in the development of erect locomotion. Of the 33 children for whom the data concerning the two functions were adequate for inspectional comparisons, the onset of the segmental plantar reflex occurred about the time of deliberate walking in 26. However, dorsiflexion of the toes was elicited occasionally as late as 4 or 5 years of age. Such digital extensor responses were not accompanied by the mass reaction characteristic of the newborn infant.

Fulton [3] stated that the Babinski sign is a typical flexion reflex, "characterized by upgoing of the great toe and simultaneous contraction of the flexors of hip, knee, and ankle." He stated elsewhere [4] that this is a point about which there is considerable controversy. It may be that those features of the plantar response which have weighed heavily in the ratings used in this study are representative of neural structures different from those involved in the Babinski phenomenon. On the other hand, some authorities [4] have claimed that the Babinski response is generally associated with the contraction of other muscles of the extremity. In any event, it is hoped that this analysis of progressive changes in the plantar response as exhibited by a group of children over a period of years may serve as a background against which pathognomonic aspects of the reflex may be more adequately appraised.

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3. Fulton, J. F.: Physiology of the Nervous System, New York, Oxford University Press, 1938, p. 101.

4. Fulton, J. F., and Keller, A. D.: The Sign of Babinski: A Study of Cortical Dominance in Primates, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

SUMMARY

Developmental changes in the infant's reactions to plantar stimulation have been analyzed. Repeated examinations were made of a group of 75 children at varying intervals during the first five years of life. On the basis of the mass and the segmental aspects of the response, it was possible to classify the reactions into three developmental phases. These sequential changes reflect reorganization or maturation of the neural mechanisms involved. The mass reflex was characteristic during the first four months, the transitional phase was predominant by about the end of the first year and the segmental reflex was common to all of the children after the age of 2½ years.

QUANTITATIVE DETERMINATION OF THE PYRUVIC ACID CONTENT OF THE BLOOD IN INFANTS AND IN CHILDREN

AN ATTEMPT TO DIAGNOSE SUBCLINICAL DEFICIENCY OF VITAMIN B_1

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AND
PEI-KUANG LI, M.D.*
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The achievements of recent years in the science of nutrition, an important part of the structure of preventive and therapeutic pediatrics, are among the most significant in the annals of medicine. From a nutritional point of view, the health of the growing child can be expressed not merely in terms of the rate of gain in body weight but in terms of the equilibrium displayed in maintaining normal body functions. Vitamin B_1 is one of the accessory dietary factors most essential to the growing child for the metabolism of foodstuffs, particularly the digestion and utilization of carbohydrate. While the state of severe avitaminosis B_1 may be rare in human beings, a cursory review of the literature published during the last decade, as summarized by Strauss,[1] reveals that relative or partial deficiency of vitamin B_1 is of common occurrence. The partial type of deficiency, which may be designated as a subclinical form of avitaminosis B_1, is so subtle in its clinical manifestations that unless vigilance is exercised in its detection it evades diagnosis. However, the latent type of vitamin B_1 deficiency responds with a remarkable rapidity to specific treatment. Thus it is a matter of greatest importance that such hypovitaminosis be promptly recognized under all circumstances, not as a primary factor in any disease picture but as a complication requiring specific therapy.

Since it is difficult, if not impossible, to diagnose the latent form of vitamin B_1 deficiency from clinical signs alone, it is here proposed that some objective measure be adopted which can be used to designate both the presence and the degree of such a deficiency. For this purpose either the direct method of measuring the quantity of vitamin B_1 present or the indirect procedure of determining the lesions which are more or less specific for hypovitaminosis may be employed (table 1). The investi-

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1. Strauss, M. B.: The Therapeutic Use of Vitamin B_1 in Polyneuritis and Cardiovascular Conditions, J. A. M. A. **110**:953 (March 26) 1938.

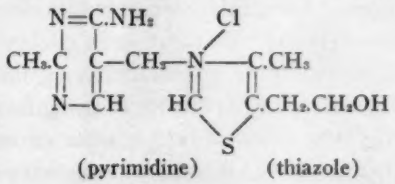
gation here reported is directed to a means of demonstrating one of the most characteristic signs of vitamin B_1 deficiency: by measurement of the concentration of pyruvic acid, a ketonic acid containing one unsaturated carbonyl group in the molecule. In subjects with vitamin B_1 deficiency this substance accumulates in abnormal amounts in the blood and tissues.

Ever since vitamin B_1 was isolated in pure form by Jansen and Donath,[2] who termed the vitamin aneurin and thereby implied its antineuritic power, the efforts of investigators have been directed chiefly toward its chemical identification and characterization. When the pure vitamin is treated with neutral sodium sulfite solution, two products are recovered, one of which is suggestive of pyrimidine and the other a substance which on oxidation with nitric acid yields a thiazole containing

TABLE 1.—*Methods for Diagnosing Vitamin B_1 Deficiency*

Direct Methods	Indirect Methods
Determination of concentration of free thiamine in blood	Chemical examination of the blood for: (1) concentration of pyruvic acid, (2) presence of methyl glyoxal (?) and (3) concentration of lactic acid
Determination of amount of free thiamine excreted in urine	Clinical manifestations: (1) anorexia, (2) polyneuritis (involving central neurons and peripheral nerves), (3) paralysis, (4) cardiac changes and (5) edema
Determination of concentration of combined thiamine (cocarboxylase) in blood (Warburg's manometric method)	
Therapeutic tests	

a stable sulfur atom. On the basis of these reactions Williams[3] established that the structural formula of vitamin B_1 is:



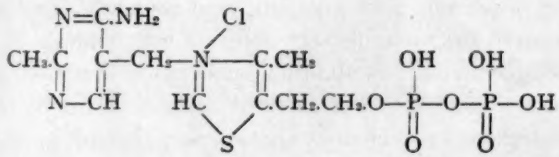
Thiamine, the name by which this vitamin is now known, was later found by Löhmann and Schuster[4] to be an enzyme which manifests its activity in its coenzyme form. The latter substance is the product of phosphorylation of thiamine; the two molecules of phosphoric acid, having been bound in the pyrophosphate form, replace the hydrogen of the

2. Jansen, B. C. P., and Donath, W. F.: Antineuritisch Vitamine, Chem. Weekbl. **23**:201, 1926; On the Isolation of the Anti-Beriberi Vitamin, Verhandl. d. k. Akad. u. wetensch. **29**:1390, 1926; Isolation of Anti-Beriberi Vitamin, Mededeel. v. d. dienst. d. volksgezondh. in Nederl. Indië **16**:186, 1926.

3. Williams, R. R.: Structure of Vitamin B_1, J. Am. Chem. Soc. **58**:1063, 1936; The Chemistry of Thiamin (Vitamin B_1), J. A. M. A. **110**:727 (March 5) 1938.

4. Löhmann, K., and Schuster, P.: Ueber die Cocarboxylase, Naturwissenschaften **25**:26, 1937; Untersuchungen über die Cocarboxylase, Biochem. Ztschr. **294**:188, 1937.

alcoholic hydroxyl group in the thiazole side chain. The structural formula of this substance is:



Phosphorylated thiamine is known as cocarboxylase, and its specific function has been established beyond any doubt as that of a coenzyme which, in conjunction with a specific protein carrier, is concerned in the oxidative decarboxylation of pyruvic acid. According to Williams,[3] in such an enzyme-coenzyme system, with a protein or proteins present in washed yeast cells, the evolution of carbon dioxide is greatly promoted when the cells are suspended in a pyruvate-phosphate medium, a phenomenon which does not take place if free thiamine alone is employed. The cocarboxylase is thought to promote the reaction as follows:

$$\underset{\text{(pyruvic acid)}}{CH_3.CO.COOH} \xrightarrow{\text{(decarboxylation)}} CH_3CHO + CO_2 \quad \underset{\text{(acetaldehyde)}}{}$$

Ever since Eijkman [5] made his classic observations on the causation of beriberi, emphasis has been laid from time to time on the perversion of the carbohydrate metabolism which accompanies this disease. It is now firmly established that vitamin B_1 deficiency is invariably associated with profound changes in the oxidative catabolism of carbohydrate. The importance of various types of unsaturation in molecules of intermediary metabolites, the carbonyl group in particular, as factors in the degradation of carbohydrate is being increasingly recognized. There seems to be little doubt of the close relation between the carbonyl compounds in the blood and in other tissues. Of these intermediary substances pyruvic acid or one of its easily hydrolyzable compounds, such as phosphopyruvic acid, is considered the most important.

Pyruvic acid was discovered by Berzelius [6] more than a century ago, and since the publication of the Embden-Meyerhof scheme (chart 2), pyruvic acid has been recognized as a normal intermediary product of carbohydrate metabolism. But the phenomenon of the accumulation of bisulfite-binding substances (carbonyl compounds), particularly pyruvic acid, in the body fluids has only recently begun to be investigated. Thompson and Johnson,[7] in a preliminary report, stated that

5. Eijkman, C.: Eine beriberiähnliche Krankheit der Hühner, Virchows Arch. f. path. Anat. **148**:523, 1897.

6. Berzelius, J. J.: Ueber die Distillationsprodukte der Traubensäure, Ann. d. Phys. u. Chem. **36**:1, 1835.

7. Thompson, R. H. S., and Johnson, R. E.: Blood Pyruvate in Vitamin B_1 Deficiency, Biochem. J. **29**:694, 1935.

avitaminosis B_1 in pigeons and in rats gives rise to an increase of bisulfite-binding substances in the blood, which is specifically related to the vitamin deficiency and is probably due entirely, in pigeons at least, to an increase in pyruvic acid. After administration of vitamin B_1 without any additional food, so as to allow the condition of starvation to remain strictly analogous to that of avitaminotic birds, the bisulfite-binding substances returned to a level only slightly above normal. The results of numerous and extensive investigations, chiefly on the brain tissue of pigeons which showed opisthotonos because of vitamin B_1 deficiency, led Peters [8] to the conclusion that the biochemical lesion specifically concerned with this type of avitaminosis is most closely related to the oxidation of pyruvic acid. This investigator was the first to demonstrate clearly the restoration of the diminished tissue respiration by the addition of minute amounts of crystalline thiamine hydrochloride in vitro to the avitaminous brain tissue. Furthermore, Platt and Lu [9] reported that there was an abnormal accumulation of the carbonyl compounds in the blood of persons with beriberi and that of these substances pyruvic acid constituted by far the largest proportion. Thus, there seems to exist a pronounced similarity between the biochemical lesions produced in animals and in human beings by vitamin B_1 deficiency. It is obvious that in all cases in which there is either a manifest or a latent state of vitamin B_1 deficiency an abnormal increase in the pyruvic acid of the blood may be expected. As Cowgill [10] has suggested, ". . . quantitative examination of this fluid [blood] for pyruvate might be made the basis of a biochemical method for detection of a state of vitamin B_1 deficiency."

The object of this investigation was first to establish the normal range of the concentration of pyruvic acid in the blood of infants and children and then to ascertain the values for persons with various diseases. An attempt has also been made to develop a simple quantitative method which may be easily employed in the average laboratory for the diagnosis of clinical and subclinical vitamin B_1 deficiency.

DEFINITION OF TERMS

To avoid possible confusion in the discussion to follow, we propose the use of the terms hypothiaminosis acuta and hypothiaminosis lenta to designate manifest (clinical) and latent (subclinical) states, respectively, of vitamin B_1 deficiency. The term athiaminosis is purposely avoided for the simple reason that strictly speaking no such condition

8. Peters, R. A.: The Biochemical Lesion in Vitamin B_1 Deficiency, Lancet **1**:1161, 1936.

9. Platt, B. S., and Lu, G. D.: Chemical and Clinical Findings in Beriberi with Special Reference to Vitamin B_1 Deficiency, Quart. J. Med. **29**:355, 1936.

10. Cowgill, G. R.: The Physiology of Vitamin B_1, J. A. M. A. **110**:805 (March 12) 1938.

as complete or total thiamine deficiency exists. Even in the instances of extreme thiamine deprivation, whether clinically encountered or experimentally produced, certain tissues always contain thiamine even though in greatly reduced amounts.

The term thiamine will be used for free vitamin B_1, while the terms thiamine pyrophosphate or diphosphothiamine will be applied to the phosphorylated compound or combined form of thiamine, now generally known as cocarboxylase.

METHOD

Of the several methods which have been used for the quantitative estimation of blood pyruvate (Clift and Cook,[11] Simon and Piaux[12] and Case[13]), the micromethod of Lu[14] appears to be the only one adapted to work with small infants and children. This technic, which is essentially a microadaptation of the original 2,4-dinitrophenylhydrazine method of Case and Neuberg, is based on the propensity of pyruvic acid to form hydrazone, which is dissolved in a solution of sodium carbonate. The intensity of the pink color which develops on addition of sodium hydroxide is determined colorimetrically against a standard. The procedure, with a slight modification, will be briefly described.

From a moderately deep puncture of the skin 0.2 cc. or less of capillary blood is obtained and quickly dropped into a centrifuge tube, previously weighed and kept at a low temperature in a vessel packed with finely shaved ice, which contains exactly 1 cc. of a 10 per cent solution of trichloroacetic acid. After thoroughly mixing the blood and the acid with a fine glass rod, the actual amount of blood is calculated by reweighing the test tube on an analytic balance. After the blood proteins have been completely precipitated (fifteen to twenty minutes) at this low temperature, the tube is centrifuged for five minutes at high speed. By means of a long glass pipe, fitted with a rubber bulb, the clear supernatant fluid containing pyruvic acid is carefully transferred to a clean test tube (tube 1). The precipitate is again treated with 1 cc. of a 5 per cent solution of trichloroacetic acid and after reagitation the tube is allowed to stand for five minutes at low temperature to remove the remaining portion of pyruvic acid. The supernatant fluid obtained from this second centrifugation is added to the contents of tube 1.

One cubic centimeter of a 0.1 per cent solution of 2,4-dinitrophenylhydrazine in a two times normal solution of hydrochloric acid is added to tube 1, and the reaction is allowed to continue at room temperature for at least ten minutes so that all of the hydrazone of pyruvic acid possible may be produced. The hydrazone is extracted with 2 cc. of ethyl acetate; after the layers have completely separated, the bottom layer is pipetted off into tube 2, the remaining acetate solution being kept in tube 1. Another 2 cc. of ethyl acetate is added to tube 2,

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11. Clift, F. P., and Cook, R. P.: A Method of Determination of Some Biologically Important Aldehydes and Ketones, with Special Reference to Pyruvic Acid and Methylglyoxal, Biochem. J. **26**:1788, 1932.

12. Simon, L. J., and Piaux, L.: Sur la caractérisation et dosage de petites quantités d'acide pyruvique, Bull. Soc. chim. biol. **6**:477, 1924.

13. Case, E. M.: The Determination of Pyruvic Acid, Biochem. J. **26**:753, 1932.

14. Lu, G. D.: Studies on the Metabolism of Pyruvic Acid in Normal and Vitamin B_1 Deficient States: A Rapid, Specific and Sensitive Method for Estimation, Biochem. J. **33**:249, 1939.

and the extraction of hydrazone is repeated as before. The bottom layer, which becomes as clear as water on complete separation of the two layers, is discarded and the remaining solution carefully added to tube 1.

Tube 2 is rinsed out with 2 cc. of a 10 per cent solution of sodium carbonate, and the contents are poured into tube 1. By means of the same pipet the top layer of the acetate is thoroughly mixed with the bottom layer of sodium carbonate. When the two layers are completely separated, the bottom layer is transferred to tube 2. The same procedure for dissolving pyruvic acid with a solution of sodium carbonate is repeated a second and a third time, the sodium carbonate layer being each time transferred to tube 2. The final acetate remaining in tube 1 is discarded; the three extractions of pyruvic acid in sodium carbonate in tube 2 total 6 cc. The final removal of any trace of hydrazone of ketonic acids other than pyruvic acid is made by the addition of 1 cc. of ethyl acetate to tube 2. When the two layers are clearly separated, the yellow bottom layer is carefully transferred to tube 3.

Four cubic centimeters of a normal solution of sodium hydroxide is added to tube 3. The pink color which develops almost instantaneously will fluctuate somewhat if any impurities are present in the mixture, but color due to substances other than pyruvic acid will disappear within ten minutes. During these ten minutes the photoelectric cell colorimeter (Evelyn[15]) is warmed to insure optimal working condition. The unknown solution is then transferred to a colorimeter cell and, with the use of filter 520, a galvanometer reading is recorded. The zero point on the galvanometer scale is set by the use of a blank which has been subjected to the identical treatment accorded the blood sample. The amount of pyruvic acid is calculated from a standard curve previously prepared by calibration of a pure solution of pyruvic acid redistilled three times in triple distilled water in accordance with the instructions given by Lu.

PYRUVIC ACID CONTENT OF THE BLOOD OF RATS WITH AVITAMINOSIS B_1

In order to test the validity of Cowgill's suggestion, previously referred to, we made a preliminary series of observations on the relation between the state of vitamin B_1 deficiency and the levels of blood pyruvate in experimental animals (rats), which were reported elsewhere.[16] The results of these observations may be briefly summarized (table 2). Twelve rats, 6 male and 6 female, were placed on a ration free of vitamin B_1 soon after they were weaned. For each animal the level of blood pyruvate was determined sometime within the three days preceding the institution of the deficiency diet. The average level of pyruvic acid in the blood was also determined for a group of normal rats and was found to range between 0.50 and 1.30 mg. per hundred cubic centimeters, with an average of 0.91 mg. It was found that with the increase in the severity of the deficiency state the concentration of pyruvic acid in the blood steadily increased, so that by the end of the first month after the initiation of vitamin deprivation the average increase of pyruvate in the blood was 250 per cent, and by the end of the second

15. Evelyn, K. A.: Stabilized Photoelectric Colorimeter with Light Filters, J. Biol. Chem. **115**:63, 1936.

16. Li, P. K., and Kato, K.: Determination of Blood Pyruvate in Vitamin B_1 Deficiency, J. Lab. & Clin. Med. **26**:1314, 1941.

month of depletion the increase was nearly 500 per cent. It was further observed that when the blood pyruvate had increased about 250 per cent (so that the level was approximately 2.5 mg. of pyruvate per hundred cubic centimeters of blood), the animals began to show definite signs of neural involvement, while with an increase of 500 per cent (to a level of approximately 5.00 mg. per hundred cubic centimeters) paralysis of the limbs developed and convulsive seizures were provoked by the slightest stimulation. One animal in which the level of pyruvate in the blood was extremely elevated (6.0 mg. per hundred cubic centimeters) failed to respond to the subsequent administration of thiamine hydrochloride and died within a few hours. But in all the other animals a single injection of the calculated minimal saturation dose (30 international units) of thiamine hydrochloride brought about a remarkable decrease in the blood pyruvate, so that by approximately eight hours

TABLE 2.—*Mean Values for Blood Pyruvate of Polyneuritic Rats*

Week of Observation	Average Level of Blood Pyruvate, Mg. per 100 Cc.			Increase, Percentage
	Males *	Females	All Animals	
Preceding experiment	0.96	0.96	0.96	.....
First	1.18	1.15	1.12	21.7
Second	2.25	2.26	2.26	135.2
Third	2.26	2.89	2.58	166.4
Fourth	3.22	3.75	3.49	263.1
Fifth	4.28	3.63	3.95	311.3
Sixth	4.14	4.50	4.32	349.5
Seventh	4.72	5.33	5.02	422.3
Eighth and after	5.61	5.62	5.62	484.8

* Six male and 6 female rats were studied.

after injection the average values had decreased by over 50 per cent of the preinjection level.

PYRUVIC ACID CONTENT OF THE BLOOD OF INFANTS AND CHILDREN

Since the experimental observations on rats indicated that the determination of the concentration of pyruvic acid in the blood can be employed as a quantitative means of expressing the degrees of hypothiaminosis, the method was used to determine the presence or absence of the subclinical, as well as the clinical, type of vitamin B_1 deficiency in infants and children.

The results of 150 determinations of the concentration of pyruvic acid in the blood of infants and children of all ages and with various pathologic conditions are presented in the scattergram (chart 1). The values for blood pyruvate were plotted according to the age of the patients, and no significant variation in the concentration of blood pyruvic acid with age was demonstrated. The great majority of values are less than 1.0 mg. of pyruvate per hundred cubic centimeters of blood, the average being 0.96 mg. With a liberal allowance for any technical

errors, therefore, it may be safe to consider the normal values for pyruvate as ranging between 0.6 and 1.0 mg. per hundred cubic centimeters of blood, with an average of 0.8 mg. Thus, in contrast to the observations on experimental animals (table 2), the values for blood pyruvate which exceed 1.0 mg. per hundred cubic centimeters are regarded as being abnormally high and indicate a state of hypothiaminosis. In table 3 the abnormally high values for pyruvic acid in the blood of patients with various pathologic conditions are listed in the order of their magnitude. The percentage occurrence of increased concentration of blood pyruvate in association with various diseases is

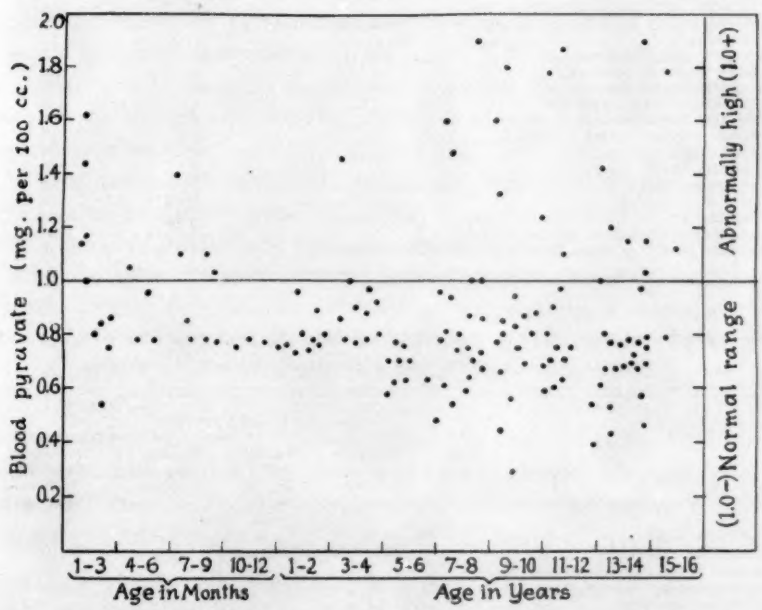

Chart 1.—Scattergram of values for the concentration of pyruvic acid in the blood in 143 determinations on children, up to 15 years of age, with various diseases. For 109 determinations the values were less than 1 mg. of pyruvic acid per hundred cubic centimeters, and for 34 they were more than 1 mg. but less than 2 mg. Values for 7 additional determinations, which were more than 2 mg., were not included in the scattergram.

indicated in table 4. It is to be noted that the number of diseases (two) associated with high values in all instances (100 per cent) is too small to permit of any definite conclusion; further determinations must be made.

COMMENT

In evaluating the results of the quantitative determination of pyruvic acid in human blood, it is first necessary to consider the metabolic significance of this carbonyl compound in the general scheme of nutrition.

From the results of biochemical investigations which have been reported in the literature, it has been clearly established that pyruvic acid is a normal intermediary metabolite in the oxidation of dextrose, representing one of the most reactive substances formed in the course of

TABLE 3.—*Pathologic Conditions Associated with High Values for Blood Pyruvate*

Pathologic Condition	Age of Patient, Years	Blood Pyruvate, Mg. per 100 Cc.
Acute leukemia (white cell count 300,000)	5	3.53
Acute leukemia (white cell count 150,000)	13	3.38
Chlorosis with malnutrition	9	2.90
Diabetes mellitus (coma)	12	2.78
Rheumatic carditis (decompensation)	11	2.68
(Same patient 24 hr. after administration of thiamine hydrochloride)	..	1.52
Rheumatic heart disease	10	2.48
Diabetes mellitus (severe)	3	2.05
Rheumatic heart disease	14	1.90
Acute hemorrhagic nephritis	8	1.90
Rheumatic heart disease	9	1.80
Diabetes mellitus (after coma)	15	1.78
Exophthalmic goiter	11	1.78
Rheumatic heart disease	7	1.60
Malnutrition	3	1.46
Pyloric stenosis	2 wk.	1.44
Marasmus	6 mo.	1.40
Hemorrhagic disease of the newborn	5 days	1.17
Condition resulting from feeding breast milk exclusively	4½ mo.	1.05

TABLE 4.—*Pyruvate Values in One Hundred and Fifty Determinations on the Blood of Infants and Children with Various Pathologic Conditions*

Pathologic Condition	Values for Blood Pyruvate: Total Number of Determinations	Number Over 1.0 Mg. per 100 Cc.	Number 1.0 Mg. per 100 Cc. or Less	Percentage of Cases in Which Blood Pyruvate Was High
Leukemia, acute	5	5	0	100
Hemorrhagic disease of the newborn	2	2	0	100
Diseases of the gastrointestinal tract	7	4	3	57.1
Cardiovascular diseases	35	16	19	45.7
Endocrine disorders	14	6	8	42.8
Nutritional diseases	14	5	9	35.7
Diseases of the genitourinary system	9	3	6	33.3
Infections	23	0	23	0
Nervous disorders	25	0	25	0
Dermatoses	6	0	6	0
Congenital malformations (except of the heart)	7	0	7	0
Miscellaneous	3	0	3	0
Total	150	41 (27.3%)	109 (72.7%)	

carbohydrate metabolism (Barron and Lyman [17]). Moreover, pyruvic acid appears to lie at the crossroad of the metabolism not only of carbohydrate but of fat and protein (Mathews [18]). The particular way in which this acid is oxidized appears to be determined by the physiologic

17. Barron, E. S. G., and Lyman, C. M.: The Metabolism of Pyruvic Acid by Animal Tissues and Bacteria, J. Biol. Chem. **127**:143, 1939.

18. Mathews, A. P.: Physiological Chemistry, ed. 6, Baltimore, Williams & Wilkins Company, 1939, p. 1282.

condition of the tissue and by its prevailing enzyme system (Barron [19]). In an extensive series of experiments Peters and his associates [20] consistently found a reduced oxygen uptake in the brain tissue of polyneuritic pigeons, a condition which can be remedied by the addition of vitamin B_1 (catatorulin action). Further investigation of the catalytic action of pure thiamine has revealed that the tissues, especially of the brain of polyneuritic pigeons, when respiring in the presence of added lactate without vitamin B_1 showed an accumulation of pyruvate which could be reduced if the vitamin was added to the system in vitro. Evidently, then, vitamin B_1 takes some definite part in the catabolism of pyruvate. Johnson and his co-workers [21] expressed the view that the accumulation of pyruvic acid in the blood may be regarded as reasonably specific for vitamin B_1 deficiency. It follows, therefore, that the pyruvic acid content of the blood should indicate the degree of thiamine deficiency and thereby furnish a means for diagnosis of this type of deficiency.

These general statements are specifically illustrated in chart 2, which depicts the important steps of glycolysis in blood and suggests the several possible products of pyruvic acid metabolism. According to this scheme, based on a widely accepted though greatly simplified conception (Burk [22]), the esterification of dextrose proceeds in a stepwise conversion of hexose into triose, which in turn gives rise to the more reactive phosphoglyceric acid, and finally pyruvic acid is produced from phosphopyruvic acid by the separation of its phosphoric acid radical. The pyruvic acid so formed is readily oxidized in animal tissues, yet little is known about the immediate products of its oxidation. It may be converted into any of a variety of substances, according to which particular enzyme system prevails under any given condition (Smyth [23]). Thus,

19. Barron, E. S. G.: Thiamine and Sulfhydryl Reactions, in Symposium in Tissue Respiration, read at the annual meeting of the American Society of Biological Chemists, New Orleans, March 15, 1940; Thiamine and Sulfhydryl Compounds, Bol. Soc. quim. de Peru **6**:7, 1940. Barron, E. S. G., and Lyman, C. M.: The Functions of Diphosphothiamine (Phosphorylated Vitamin B_1), Science **92**:337, 1940.

20. Passmore, R.; Peters, R. A., and Sinclair, H. M.: On Catatorulin: A New Method of Comparing the Oxidative Factor in Vitamin B_1 Concentrate, Biochem. J. **27**:842, 1933. Kinnersley, H. W.; O'Brien, J. R., and Peters, R. A.: Crystalline Vitamin B_1, ibid. **29**:701, 1935.

21. Johnson, R. E.; Meiklejohn, A. P.; Passmore, R., and Thompson, R. H. S.: A Note on the Level of Carbonyl Compounds in Human Blood, Biochem. J. **29**: 2506, 1935.

22. Burk, D.: A Colloquial Consideration of the Pasteur and Neo-Pasteur Effects, in Cold Spring Harbor Symposia on Quantitative Biology, Cold Spring Harbor, L. I., New York, The Biological Laboratory, 1939, vol. 6, p. 420.

23. Smyth, D. H.: The Oxidation of Pyruvate by Heart Muscle, Biochem. J. **34**:1046, 1940.

it may be directly oxidized into carbon dioxide and water or reduced to lactic acid in tissue or to ethyl alcohol in alcoholic fermentation. In the presence of an adequate supply of thiamine and its pyrophosphate, pyruvic acid is converted by oxidative decarboxylation into acetaldehyde and then into carbon dioxide and water. It is also capable of forming citric acid in the breast muscle by the intervention of the C_4-dicarboxylic acids (the citric acid cycle of Krebs and Johnson [24]). Clearly, then, a lack of thiamine, particularly of diphosphothiamine, will seriously hinder the normal disposal of this acid and will result in pyruvic acid acidosis. According to Krebs and his associates,[25] pyruvic acid is removed anaerobically in various tissues besides the breast muscle under normal conditions, the testis having the highest rate of removal and such tissues

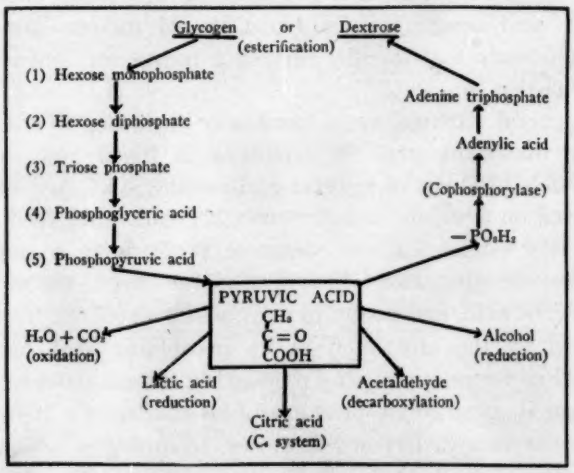

Chart 2.—Glycolytic cycle in the blood, showing the key position occupied by pyruvic acid with reference to several possible reactions.

as brain, liver and kidney following in the order of speed in catalytic dissipation of this ketonic acid. While the rate of conversion of pyruvate varies considerably in different tissues, the concentration of this acid in the blood appears to remain at a fairly constant level and offers a clinically available index of thiamine action in the organism as a whole. It is for this reason that we propose the use of a method for determining the pyruvic acid concentration in the blood as a means of diagnosing both manifest and latent types of hypothiaminosis in clinical practice.

The results of determinations of pyruvic acid in the blood here presented bring out several points of clinical significance. First it is

24. Krebs, H. A., and Johnson, W. A.: Role of Citric Acid in Intermediate Metabolism in Animal Tissues, Enzymologia **4**:148, 1937.

25. Krebs, H. A., and Johnson, W. A.: Metabolism of Ketonic Acids in Animal Tissues, Biochem. J. **31**:645, 1937. Krebs, H. A., and Eggleston, L. V.: The Oxidation of Pyruvate in Pigeon Breast Muscle, ibid. **34**:442, 1940.

to be noted that of the total of 150 analyses of blood which were made the concentration of pyruvic acid was found to be less than 1.0 mg. per hundred cubic centimeters in approximately three fourths (72.7 per cent) but that the remaining one fourth (27.3 per cent) gave values definitely greater than 1.0 mg. If 0.8 mg. of pyruvate per hundred cubic centimeters of blood is accepted as the normal average, the values above this level are decidedly abnormal. Yet none of the patients exhibited signs or symptoms in any way resembling those of beriberi; therefore their condition must be regarded as latent hypothiaminosis. These determinations were made for children of all ages with a variety of pathologic conditions; so the results suggest the probable incidence of latent thiamine deficiency in the average pediatric practice. Hypothiaminosis in these patients may have originated in a number of ways, but the common factor is inadequacy of vitamin B_1, due either to an inadequate intake or to an increased need of thiamine because of an accelerated metabolic rate. It is well known that such complications as anorexia, vomiting and the more serious disturbances of the gastrointestinal tract are apt to produce thiamine deficiency because of the impaired utilization of the vitamin. Accelerated metabolism, so frequently encountered in febrile diseases and in certain disorders of the endocrine glands, particularly hyperthyroidism, also creates an increased demand for vitamin B_1. In the presence of either impaired absorption of the vitamin or accelerated metabolism, pyruvic acid tends to accumulate in the blood as well as in the tissues.

All of the blood analyses made in 2 cases of acute leukemia and 2 cases of hemorrhagic disease of the newborn yielded abnormally high values for the pyruvic acid concentration. In fact, the highest value (3.53 mg. of pyruvate per hundred cubic centimeters of blood) in the entire series was obtained in a case of acute stem cell leukemia in which there was a white cell count of 300,000 per cubic millimeter of peripheral blood. It has been shown by Goodhart and Sinclair [26] that the cocarboxylase content of the blood of patients with myelogenous leukemia is much higher than that of blood of patients with lymphatic leukemia. It appears, furthermore, that the synthesis of cocarboxylase within the cell is more complete in mature granulocytes than in immature forms. The blood in our 2 cases of acute leukemia contained large numbers of stem cells with no differentiation of specific granules. Thus, in enzyme action these predominating immature cells behave like lymphocytes, and in clinical practice cases in which there is such a blood picture are often mistaken for instances of acute lymphatic leukemia. Since autopsy in both of our cases of leukemia revealed pronounced hyperplasia of myeloid tissues, with widespread infiltration in many organs, it is reasonable to interpret the abnormally high concentrations

26. Goodhart, F., and Sinclair, H. M.: Deficiency of Vitamin B_1 in Man as Determined by the Blood Cocarboxylase, J. Biol. Chem. **132**:11, 1940.

of blood pyruvate in such cases as arising out of a deficiency in cocarboxylase, with consequent great impairment of the carbohydrate metabolism. In the 2 cases of hemorrhagic disease of the newborn the abnormal increase in blood pyruvic acid was probably brought about by a state of hypothiaminosis, in conjunction with deficiencies of other vitamins, which obtains during the neonatal period. But since practically nothing is known of the normal concentration of blood pyruvate in newborn infants, it is impossible to derive any conclusion from these limited observations. But it is at least reasonable to assume that a relative deficiency state actually exists in many newborn infants, since during pregnancy the mother frequently suffers from a lack of vitamin B_1 because of the increased demand for this vitamin incident to the development of the fetus. While the number of cases studied is limited, our results indicate that hypothiaminosis is present in many such infants and that appropriate therapy should be employed to relieve the condition.

The association of a high pyruvic acid content of the blood with conditions in which there are disorders of the gastrointestinal tract, including malnutrition, is significant, and the mechanism of its causation is simply explained. The two factors responsible for the development of hypothiaminosis are inadequate intake of the vitamin and its impaired absorption and utilization. Dann and Cowgill [27] stated that moderate diarrhea, which is a frequent complication of this class of diseases, can decrease the absorption of the vitamin B_1 ingested by 50 to 70 per cent. For patients with disorders of the gastrointestinal tract parenteral injection of thiamine hydrochloride may be required, since anorexia, vomiting and functional derangement of the stomach and intestines can make oral administration impracticable.

An abnormal accumulation of blood pyruvate has also been found to occur in a relatively high percentage of cases of both acute and chronic rheumatic heart disease. While the exact nature of the disturbance in carbohydrate metabolism in this disease is not clear, it is interesting to recall that Weiss [28] and Weiss and Wilkins [29] drew attention to the frequent association of vitamin B_1 deficiency with many types of heart disease and that Ohta [30] and Waring [31] found cardiac enlargement due to avitaminosis in infants and children was of not infrequent occurrence.

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27. Dann, M., and Cowgill, G. R.: The Influence of Diarrhea on the Vitamin B_1 Requirement, Arch. Int. Med. **62**:137 (July) 1938.

28. Weiss, S.: Vitamin B and Cardiac Failure, Clin. Med. & Surg. **44**:353, 1937.

29. Weiss, S., and Wilkins, R. W.: The Nature of the Cardiovascular Disturbances in Vitamin Deficiency States, Tr. A. Am. Physicians **51**:341, 1936; The Nature of the Cardiovascular Disturbances in Nutritional Deficiency States (Beriberi), Ann. Int. Med. **11**:104, 1937.

30. Ohta, K.: Zur Klinik der Säuglingsberiberi, Jahrb. f. Kinderh. **128**:1, 1930.

31. Waring, J. I.: Beriberi in Infants, Am. J. Dis. Child. **38**:52 (July) 1929; Nutritional Heart Disease in Children, ibid. **55**:750 (April) 1938.

All these observers found that the administration of vitamin B_1 was accompanied by noticeable clinical improvement.

By far the most important group of conditions in which there is evidence of subclinical thiamine deficiency are those due to endocrine disturbances. In cases of diabetes mellitus the elevation of pyruvic acid in the blood is readily explained on the basis of ketosis resulting from derangement of the carbohydrate metabolism, of which avitaminosis may be an important complication (Wohl [32]). Diabetic acidosis is primarily due to an accumulation of the acetone bodies, some of which may give the same color reaction as that of pyruvic acid. But in the micromethod of Lu the final solution is allowed to stand for ten or fifteen minutes before the colorimeter reading is taken and the dilute port wine color utilized eliminates all reactions except that of pyruvic acid. Other intermediary products of carbohydrate metabolism react with bisulfite and also, to some extent, give a similar color reaction when converted into hydrazones, but with one exception they can all be eliminated by the procedure described. This one exception is the color due to the presence of alphaketoglutaric acid, but such minute quantities of this substance are present that for practical purposes it may be disregarded. It is also interesting to note that extremely high values for blood pyruvate were found for children with diabetes during severe acidosis, either with or without coma. For obese children the values for blood pyruvate were consistently low. In cases of hyperthyroidism the pyruvic acid content of the blood was frequently high; the hypothiaminosis which supposedly is associated with this condition is directly due to the increased metabolic rate, as was shown experimentally by Cowgill and his associates.[33]

In some diseases of the genitourinary system the concentration of pyruvic acid in the blood is above normal, as was demonstrated in the 2 cases of acute hemorrhagic nephritis. The explanation of the mechanism responsible for the production of hypothiaminosis in this disease is purely speculative, but it is within reason to believe that accumulation of pyruvate in the blood may result from impaired excretion of the acid in the urine. On the other hand, in 1 case of nephrosis, in which repeated determinations were made, the concentration of pyruvic acid in the blood was consistently low, even during the terminal stage.

Finally, reference must be made to the effect of thiamine on the concentration of pyruvic acid in the blood. In a few cases of pyruvic

32. Wohl, M. G.: Avitaminosis in the Course of Diabetes: Occurrence in a Case, with Symptoms and Lesions of Beriberi Predominating, J. A. M. A. **87**: 901 (Sept. 18) 1926.

33. Himwich, H. E.; Goldfarb, W., and Cowgill, G. R.: Studies in the Physiology of Vitamins: XVII. The Effect of Thyroid Administration upon the Anorexia Characteristic of Lack of Undifferentiated Vitamin B, Am. J. Physiol. **99**:689, 1932. Cowgill, G. R., and Palmieri, M. L.: Studies in the Physiology of Vitamins: XXII. The Effect of Experimentally Induced Hyperthyroidism on the Vitamin B Requirement of Pigeons, ibid. **105**:146, 1933.

acid acidosis we administered thiamine hydrochloride with the purpose in view of studying the changes in blood pyruvate concentration which would ensue. An 11 year old girl with rheumatic heart disease was observed in the hospital for several weeks. In the terminal stage, marked generalized edema with pericardial effusion developed. The level of blood pyruvate was markedly elevated (2.68 mg. per hundred cubic centimeters). After the subcutaneous administration of 1 mg. (300 international units) of thiamine hydrochloride, the blood pyruvate decreased to a level of 1.52 mg. per hundred cubic centimeters within twenty-four hours. For a 6 year old boy who had acute leukemia, with a leukocyte count of 300,000 cells per cubic millimeter of peripheral blood, the blood pyruvate was found to be 2.05 mg. per hundred cubic centimeters. One milligram of thiamine hydrochloride was given by hypodermic injection, and in twenty-four hours the level was reduced to 1.88 mg. per hundred cubic centimeters. Although both of these patients died as the direct result of the primary diseases from which they suffered, the subclinical vitamin B_1 deficiency was definitely alleviated by the administration of thiamine hydrochloride. These observations make it clear that hypothiaminosis lenta may be associated with various diseases of infants and children and that the administration of the specific vitamin may be required as a part of the therapy of any disease.

SUMMARY AND CONCLUSIONS

A new chemical method is reported for the diagnosis of vitamin B_1 deficiency. It consists of determining the concentration of pyruvic acid in the blood by the micromethod of Lu, with slight modifications.

Of a total of 150 determinations of the concentration of pyruvate made on the blood of infants and children of all ages and with diverse diseases and conditions, approximately one fourth (27.3 per cent) were abnormally high, indicating a state of relative thiamine deficiency.

Since there were no signs or symptoms of clinical beriberi in any of the cases in which there was an abnormally high concentration of pyruvic acid in the blood, they must be instances of hypothiaminosis of varying degrees. For the purpose of definition, we propose the use of the terms hypothiaminosis acuta and hypothiaminosis lenta to designate manifest (clinical) and latent (subclinical) states, respectively, of vitamin B_1 deficiency.

The accumulation of abnormal amounts of pyruvic acid in the blood and tissues indicates a deficiency of vitamin B_1, which in its phosphorylated form (cocarboxylase) is the specific catalytic mediator in the oxidative decarboxylation of pyruvic acid. As long as a sufficient amount of activated phosphoric acid is present in the red cells, the esterification of dextrose appears to proceed normally until the pyruvic acid stage is reached. The deficiency of cocarboxylase, however, seems

to impede a further degradation of pyruvic acid. While the accumulation of this carbonyl compound in itself may not give rise directly to clinical manifestations, it is fundamentally responsible for the impairment of cellular metabolism in vital organs. The functional disturbances so produced are the immediate cause of many of the symptoms of thiamine deficiency.

It therefore follows that the diseases of infants and children with which there is associated subclinical thiamine deficiency require the administration of adequate amounts of thiamine in either the free or the phosphorylated form.

ADDENDUM

Since this paper was submitted for publication, several articles have appeared bearing directly on the determination of pyruvate in the blood. Bueding and Wortis [34] found that the decrease in pyruvic acid occurring in the course of the chemical analysis of blood can be prevented by the use of a 0.2 per cent solution of sodium monoiodoacetate. It has been our experience, however, that if the sample of blood is drawn from a freely flowing puncture wound, immediately introduced into the tube of trichloroacetic acid kept at a temperature near 0 C. (32 F.) and at once agitated to precipitate the proteins, little or no decrease in pyruvic acid occurs. Such decrease is apt to take place only when much time is wasted in the technical procedure; the micromethod we use requires only from ten to fifteen seconds from the moment the blood is aspirated into the micropipet until the sample is completely mixed with the cold trichloroacetic acid. The temperature regulation is of critical importance, since at room temperature the enzyme will continue to break down the pyruvic acid. At any rate, the average value for blood pyruvate for normal children, as determined by the method of Bueding and Wortis, reported by Wortis, Goodhart and Bueding,[35] is identical with the average result which we have obtained (0.96 mg. of pyruvic acid per hundred cubic centimeters of blood), even though no iodoacetate was used in any of our determinations.

In analyzing samples of blood from patients with diabetic acidosis, Klein [36] encountered certain inaccuracies in his results due to the presence of acetoacetic acid in the blood. He found that using tungstic acid in place of trichloroacetic acid to precipitate the proteins and allowing the ethyl acetate extract to stand over night eliminated such errors. This timely suggestion should be utilized in the analyses of samples of blood from diabetic patients.

34. Bueding, E., and Wortis, H.: Stabilization of Pyruvic Acid in the Blood, J. Biol. Chem. **133**:585, 1940.

35. Wortis, H.; Goodheart, R. S., and Bueding, E.: Cocarboxylase, Pyruvic Acid and Bisulfite-Binding Substances in Children, Am. J. Dis. Child. **61**:226 (Feb.) 1941.

36. Klein, D.: Determination of Pyruvic Acid in Blood in the Presence of Acetoacetic Acid, J. Biol. Chem. **137**:311, 1941.

EXPOSURE OF TUBERCULIN-SENSITIVE CHILDREN TO EXOGENOUS INFECTION WITH HUMAN TUBERCLE BACILLI

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The role of allergy in the pathogenesis of tuberculosis remains a controversial subject. Extensive studies on this problem have led to the separation of workers in the field into two definite schools. One group is composed of those who, following the teachings of Pirquet, maintain that a person who has passed through a primary tuberculous infection, as evidenced by roentgenograms and positive reactions to cutaneous tuberculin tests, is better able to withstand future exogenous infections.[1]

Wallgren [1a] wrote:

> There is no doubt that those children who have successfully passed through a primary tuberculosis are to be regarded as a picked group, who, when exposed to a tuberculous infection, are in a more favorable position than uninfected children. It is generally found that children who are tuberculin-positive do not run any risk, if they are exposed to tuberculous infection.

The opposing school contends that the primary tuberculous infection, regardless of outcome, is a detriment since it sensitizes the tissues and renders the person susceptible to severe allergic disturbances if reinfection occurs.[2]

The leading exponents of the latter view are the workers at the Lymanhurst School, in Minneapolis, who recently reported the results of an eleven year study. Myers,[2e] writing on the experience in this

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1. (*a*) Wallgren, in Miller, J. A., and Wallgren, A.: Pulmonary Tuberculosis in Adults and Children, New York, Thomas Nelson & Sons, 1939, pp. 109 and 113. (*b*) Kjer-Petersen, R., and Ostenfeld, J.: Ugesk. f. læger **89**:257, 1927. (*c*) Heimbeck, J.: Acta med. Scandinav., 1928, supp. 26, p. 226.

2. (*a*) Myers, J. A.: Recent Facts on Transmission of Tuberculosis, J. A. M. A. **97**:316 (Aug. 1) 1931. (*b*) Stewart, C. A.: Pulmonary Diseases: 5,816 Cases in Children, with Special Reference to Childhood Type of Pulmonary Tuberculosis, Am. J. Dis. Child. **43**:803 (April) 1932; (*c*) Does Primary Tuberculosis Afford Adequate Protection Against Consumption? J. A. M. A. **100**:1077 (April 8) 1933. (*d*) Myers, J. A.: Am. Rev. Tuberc. **28**:793, 1933; (*e*) Tuberculosis Among Children and Young Adults, Springfield, Ill., Charles C. Thomas, Publisher, 1938, p. 250. (*f*) Ch'iu, P. T. Y.; Myers, J. A., and Stewart, C. A.: Fate of Children with Primary Tuberculosis, J. A. M. A. **112**:1306 (April 8) 1939.

school, stated: "Regardless of when it develops, the first infection type leaves the body in a hazardous condition from the standpoint of the development of the reinfection type of tuberculosis" (whether the reinfection is endogenous or exogenous).

To date the statistical data presented to support both premises either have been insufficient or have reflected a lack of adequate controls. Those who contend that allergy is a protective mechanism have not followed-up a controlled series of patients into and through puberty. The authors who hold that allergy is a danger have followed up their patients into puberty but have been unable to estimate with any degree of accuracy the magnitude of the exposure to tuberculosis.

The workers at Lymanhurst [2f] have summarized the results of their eleven year study as follows:

	Number	Average Age at Onset, Yr.	Sick with Reinfection Tuberculosis at End of 11 Years		Mortality Ratio of Positive Reactors to Negative Reactors
			Number	Percentage	
Children with positive reactions to tuberculin	446	7	67	15.02	38 : 1
Children with negative reactions to tuberculin	772	6.7	13	1.68	

These results are open to the following questions:

1. Is it not possible that the children with positive reactions to tuberculin, who presumably were subjected to greater exposure before study of them was begun, continued to be more exposed during the following years? There is no precise information as to the amount of exposure to tuberculosis in the two groups, although it was stated that ". . . the exact amount of exposure is impossible to estimate, but the general impression is that there is no material difference between the two groups."

2. Is it not reasonable to postulate that of the two groups of children —the one composed of those who had previously harbored tubercle bacilli in their bodies and the other of those free from infection, both groups being protected from subsequent exogenous tuberculous infections—more tuberculosis will develop among those harboring tubercle bacilli as the result of endogenous reinfections?

Two further questions, therefore, remain to be answered: First, is a child allergic to tuberculin protected, or does his tissue sensitivity render him more susceptible to the more feared reinfection, or adult, type of tuberculosis? Second, is reinfection tuberculosis the result of exogenous or endogenous infection, or may it result from either?

A study of the possible protection of infants against tuberculosis by inoculation with BCG prior to exposure, which was carried out by the Department of Health of New York City, Bureau of Laboratories,

afforded an opportunity to investigate the first question, namely, the relation between sensitivity to tuberculin and subsequent exposure to exogenous tuberculous infection, since sensitivity to tuberculin follows inoculation with BCG in almost every instance.

It was found that the sensitivity to tuberculin which followed intradermal inoculation with 0.15 mg. of BCG was retained for over two years by approximately 89 per cent of the children, for over three years by 67 per cent and for over four years by 53 per cent (these were children with no known exposure to tuberculosis). This sensitivity is only slightly less intense than that produced by inhalation of human tubercle bacilli, if one accepts the reaction to intradermal testing with 0.1 mg. of tuberculin as a reliable criterion.

FACTORS TO BE CONSIDERED IN A TUBERCULOSIS STUDY

The many variables which may influence the inception and clinical course of the disease make the accurate study of the exposure to and the subsequent development of tuberculosis in human beings difficult. Not only must the controls for comparison be carefully selected, but the following factors must be considered.

General Factors.—Among the general factors which must be taken into account are (1) the age at first exposure, (2) the intelligence and cooperation of the parents, (3) racial differences, (4) the reliability of the diagnosis made at death, (5) the adequacy of the number of patients studied, so that the effect of a result due to chance distribution may be minimized, and (6) the uniformity of the periods of study—all patients should be studied during the same period.

Conditions of Exposure.—In evaluating the exposure to tuberculosis (1) the frequency of exposure, (2) the intensity of exposure, (3) the amount of sputum expectorated by the contact and the number of tubercle bacilli it contains and (4) the portal of entry of the organism must be considered.

Environmental Conditions.—There should be no difference in the types of localities from which the patients come. They should be selected from sections in which similar racial, economic and social factors prevail.

MATERIAL AND METHODS

During the past thirteen years a study of children exposed to tuberculosis has been carried on in New York city by the Bureau of Laboratories of the Department of Health. The observations reported in this paper were collected in the course of an intensive investigation of the efficacy of BCG in immunization against tuberculosis. During the thirteen years 2,074 children have been studied, of whom 1,005 were vaccinated and 1,069 held as controls.

All of the children were referred to the Bureau of Laboratories from various tuberculosis clinics and hospitals in New York city. They were all from tuberculous families and, with rare exceptions, were placed under observation before they were 12 months of age.

The children were followed closely; they received monthly visits by the nurses to their homes, frequent physical examinations and, with few exceptions, roentgenographic examinations and cutaneous tests with tuberculin at three to six month intervals throughout the period of study. The cutaneous tests were performed by one of the staff pediatricians with freshly diluted old tuberculin furnished by the Department of Health of New York City. The routine dose was 0.1 mg. given intradermally, the dose being raised to as high as 10 mg. in certain instances. The reactions were read and measured at the end of forty-eight hours by specially trained nurses. Preliminary tests with tuberculin, in which up to at least 1 mg. was used, were performed for all of the children, and roentgenograms of the chest were taken for most of them, except those whose study was begun at birth.

TABLE 1.—*Exposure of Children to Tuberculosis in Vaccinated and Control Groups*

		Duration of Exposure					
		Under 6 Months		6-12 Months		Over 12 Months	
	Total	Number	Percentage	Number	Percentage	Number	Percentage
Controls exposed to persons with positive sputum	231	95	41.1	47	20.3	89	38.6
Vaccinated children exposed to persons with positive sputum	251	70	28.0	69	27.6	112	44.6
Controls exposed to persons with negative sputum	245	18	7.3	15	6.1	212	86.5
Vaccinated children exposed to persons with negative sputum	212	16	7.5	22	10.3	174	82.0

Since Jan. 1, 1933 alternate patients have been selected for controls and for study,[3] those chosen for study being vaccinated intradermally with 0.15 mg. of BCG. Only these groups will be considered in this paper.

The control group comprised 476 children with an initially negative reaction to tuberculin who were later exposed to patients with open tuberculosis. The inoculated group comprised 463 children similarly exposed who became sensitive to tuberculin from vaccination with BCG, as evidenced by a positive reaction to the Mantoux test within three months of vaccination.[4]

RESULTS

Before the comparative mortality rates from tuberculosis of the two groups of children were accepted as valid, it was essential to ascertain the comparable status of the two groups in terms of exposure (table 1).

3. Levine, M. I.; Vogel, P., and Rosenberg, H. A.: Am. Rev. Tuberc. **38**: 632, 1938.

4. It is possible that a few of the children were harboring a tuberculous infection and were in the preallergic phase at the time of vaccination.

It is evident from the table that the proportion of children exposed and the duration of exposure in the two groups were approximately the same.

During the period of observation a positive reaction to tuberculin developed in 93 of the 476 controls. Since these children had initially negative reactions to tuberculin, they must have become infected during the period of observation, and this situation thus afforded an opportunity to observe the effect of infection on nonallergic persons (table 2).

In the 463 children inoculated with BCG a positive reaction to tuberculin developed within three months, presumably from the vaccination.

TABLE 2.—*Data for Controls Who Acquired a Positive Reaction to Tuberculin*

	Total	Controls Who Acquired Positive Reaction to Tuberculin		Year During Which Reaction to Tuberculin Became Positive				
		Number	Percentage	First	Second	Third	Fourth	Fifth
Controls exposed to persons with positive sputum	231	67	29.0	20	29	12	4	2
Controls exposed to persons with negative sputum	245	26	10.6	2	14	8	1	1

TABLE 3.—*Mortality from Tuberculosis in Control and Vaccinated Groups*

	Total	Number Who Acquired Positive Reaction to Tuberculin	Deaths from Tuberculosis	
			Number	Percentage
Exposed to persons with positive sputum				
Controls	231	67	5	2.16
Vaccinated children	251	251	4	1.6
Exposed to persons with negative sputum				
Controls	245	26	1	0.04
Vaccinated children	212	212	1	0.05

Since the conditions of exposure were fairly parallel to those of the controls, it is reasonable to assume that a similar proportion of children in this group were superinfected with human tubercle bacilli. If such is the case, an opportunity is made available for determining the effects of an exogenous tuberculous infection on infants already allergic to tuberculin.

A comparison of the mortality rates in the two groups during the six years of observation should serve to assess the potentialities of the danger that an exogenous infection will run a fatal course in a person rendered allergic to tuberculin (table 3).

It is obvious from the table that the difference in mortality in the two groups is within the limits of error, with the sensitized children (inoculated with BCG) showing the slightly lower mortality.

Before accepting the results, however, an analysis was made of the proportionate racial components, the ages and the period of observation of the two groups, and they were found to be parallel with the exception of the racial components. Negro and Puerto Rican babies comprised 41.8 per cent of the vaccinated group as against 31.2 per cent of the control group. Despite this variation the mortality in the vaccinated group did not exceed that in the control group (table 4).

The data, although admittedly limited, support the opinion that infants sensitive to tuberculin do not respond to an exogenous infection with human tubercle bacilli with a higher mortality from tuberculosis than do infants whose tissues are not as yet sensitive to tuberculin.

It is also of interest that in the children sensitized by inoculation with BCG considerably fewer roentgenographically evident pulmonary

TABLE 4.—*Racial Components of Control and Vaccinated Groups of Children Exposed to Persons with Positive Sputum*

	Total	Number Who Acquired Positive Reaction to Tuberculin	Deaths from Tuberculosis
Controls			
White	159	46	1
Negro and Puerto Rican	72	21	5*
Vaccinated children			
White	146	All after vaccination	3
Negro and Puerto Rican	105		2

* Four of these 5 patients died in infancy, before an adequate number of tuberculin tests could be performed.

lesions developed than in those not vaccinated,[5] presumably because the vaccination itself constitutes the primary focus of infection. Furthermore, the pulmonary lesions which did appear in the roentgenograms of the artificially sensitized group were no more severe morphologically, as evidenced by the size of the infiltration or the formation of cavities, than those of the controls.

It is difficult to evaluate the roentgenographic data in terms of a primary or a reinfection type of lesion, since again the definition of the terms is under dispute. Some writers maintain that the primary phase of tuberculosis lasts only until the sensitivity to tuberculin develops, whereas others consider as the primary phase the period extending from the time at which the first implantation of tubercle bacilli takes place in the lungs to the time at which calcification is complete or death occurs from progression of the primary complex.

5. Kereszturi, C.; Park, W. H., and Logie, A. J.: Nat. Tuberc. A. Tr. **31**: 97, 1935.

Although it is difficult to differentiate the primary and reinfection forms of pulmonary lesions by postmortem examination or roentgenogram, there were no differences noted in the severity of the lesions occurring in the two groups.

In the vaccinated group 4 of the 5 deaths were due to miliary tuberculosis; the fifth death was due either to tuberculosis or to cerebral hemorrhage as a result of pertussis. In the latter case the exact cause of death could not be determined because the extent of the autopsy was limited. In only 2 of the 5 cases were pulmonary cavities found, but in both the cavities were the result of progressive primary foci. The average age at death was 12 months.

In the control group 5 of the 6 deaths were due to miliary tuberculosis; the sixth death was the result of a primary lesion which progressed to form a large cavity. One other cavity also developed from a progressive primary focus, which eventually led to death from miliary tuberculosis. The average age at death was 12½ months.

These results, then, militate against the concept that the exogenous infection with tubercle bacilli of persons already allergic to tuberculin gives rise to a more severe type of tuberculosis, judged by the frequency and severity of the lesions or by the mortality rate, regardless of the age when infection occurs.

The results obtained from this series of cases indicate, therefore, that in children under the age of 6 years (*a*) the implantation of exogenous tubercle organisms on allergic tissue does not necessarily lead to the development of the reinfection type of tuberculosis, which is usually found during and after puberty, and does not produce lesions which give roentgenographic evidence of greater severity and (*b*) the mortality from tuberculosis among tuberculoallergic children exposed to exogenous tuberculous infection is no greater than that of nonallergic children exposed during approximately the same period.

These observations receive support from those of Opie, Flahiff and Smith,[6] who reported on their studies of protective inoculation against human tuberculosis with heat-killed tubercle bacilli. (This "vaccine" has the property of effecting a fairly stable sensitization to tuberculin of the tissues of the person inoculated.) Their study was conducted in the Mental Hospital of Kingston, Jamaica, West Indies, an institution with a high incidence of tuberculous infection. They selected for study only those patients who had negative reactions to tuberculin on admission; alternate patients were given heat-killed tubercle bacilli, the others being observed as controls. The authors reported an apparent protection of those sensitized to tuberculin before exposure—a definite decrease not only in the morbidity but in the mortality from tuberculosis.

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6. Opie, E. L.; Flahiff, E. W., and Smith, H. H.: Am. J. Hyg. **29**:155, 1939.

SUMMARY

The response of tissues which are allergic to a subsequent tuberculous infection has been the subject of many contradictory reports. One group of writers holds that in such sensitized tissue a distinct protection has developed, while the other group maintains that such tissue has increased susceptibility to a severe and dangerous reaction on reinfection with tuberculosis.

To determine the validity of these views a group of 939 children who had negative reactions to tuberculin tests and who came from tuberculous families was studied over a period of two to six years. Alternate patients (463) were sensitized to tuberculin by intradermal inoculation with 0.15 mg. of BCG. The remainder (476) served as controls. All of the children were subsequently exposed to tuberculosis.

During the period of observation 251 vaccinated (sensitized) children and 231 controls were exposed to persons with positive sputum. The remainder were exposed to persons with negative sputum. In 93 of the controls positive reactions to tuberculin developed.

Of the children sensitized with BCG and exposed to persons with positive sputum, 4, or 1.6 per cent, died of tuberculosis, whereas of the controls similarly exposed, 5, or 2.6 per cent, died of the disease.

CONCLUSIONS

The evidence obtained from this study, carried out under carefully controlled conditions over a six year period, indicates that in children under the age of 6 years the implantation of exogenous tubercle bacilli on pulmonary tissue sensitive to tuberculin does not result in a more violent tissue response or in an increase in the mortality rate.

Case Reports

LEAD ENCEPHALOPATHY SIMULATING DIFFUSE SCLEROSIS IN A CHINESE INFANT

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Recently an opportunity was afforded of studying clinically and histologically the case of a Chinese infant in which the initial diagnosis was diffuse cerebral sclerosis.

REPORT OF A CASE

The patient, a Chinese boy born April 20, 1937, was admitted to the general hospital on Dec. 13, 1939. He was born normally, the sixth child of healthy parents. The first and the second sibling had died of convulsions when they were 1 year old; the third died of diarrhea when 1 month old; the fourth, now 7 years of age, is healthy; the fifth, who died when 5 years old, was initially normal but later walking was impaired and his legs grew stiff so that shortly before his death even sitting was impossible. A seventh child, 7 months old at the time my patient was admitted to the hospital, was healthy.

For about seven months the patient's legs had been growing increasingly stiffer. Walking had been impaired for a long time, and during the last four months it had been impossible even with help. For the last four months the arms had shown signs of spastic paresis, the movements of the arms were ataxic, and a tremor was seen when the child tried to grasp anything; grasping finally became impossible. Speech had become blurred during the last few months. The child previously had suffered from fever and from measles. He had developed normally and had not been vaccinated.

Examination on admission revealed spastic tetraplegia, with flexed arms and extended legs, high muscular tonus and pathologic plantar reflexes. There were many muscular twitchings.

The temperature became high, and the patient died about twenty hours after admission.

Autopsy.—The brain was soft. The circle of Willis was normal; the cerebral white matter was somewhat yellowish, and around the lateral ventricles it was abnormally firm.

Histologic Examination.—In the white matter severe, diffuse demyelination was noted especially in the cerebral hemispheres (fig. 1), and the corticofugal systems (fig. 2) and the white matter around the dentate nucleus were also involved. At the same places swelling and granulation of the protoplasm of the oligodendroglia cells and large gemästete (mast) glia cells were present. In the most severely damaged areas not a single normal oligodendrocyte could be found.

The swollen oligodendrocyte in sections prepared with sudan stain were yellowish, like the surviving myelin sheaths, not orange, like some fat granule cells and small deposits of lipoid along the vessels. In Weigert-Pal preparations the granules took the same color as the myelin sheaths (fig. 3); therefore they must be supposed to consist of myelin not yet broken down to lipoids.

From the Department of Neuropathology, School of Medicine.

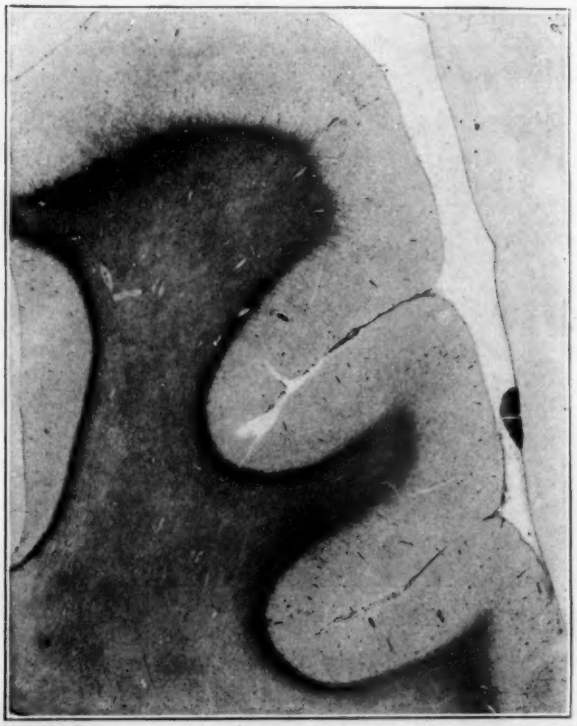

Fig. 1.—Section of a cerebral convolution stained by the Weigert-Pal method. The U fibers are more or less preserved, while the central fibers are almost totally degenerated. Low magnification.

Fig. 2.—Section of cervical segment of the spinal cord, showing the degeneration of both lateral and anterior pyramidal tracts. The staining and magnification are the same as those in figure 1.

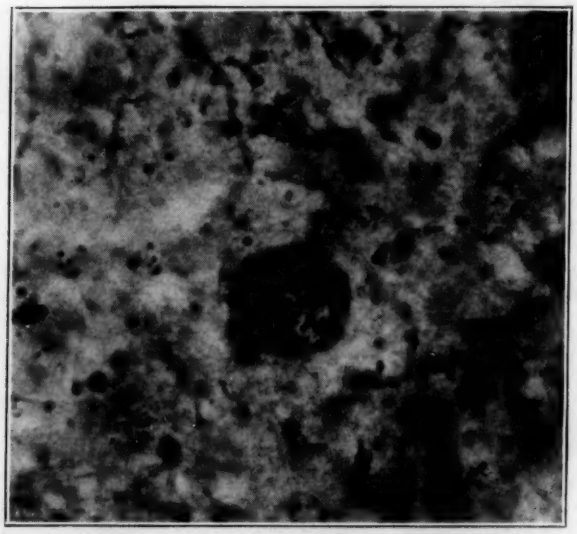

Fig. 3.—Oligodendrocyte, stained with the Weigert-Pal technic; × about 750.

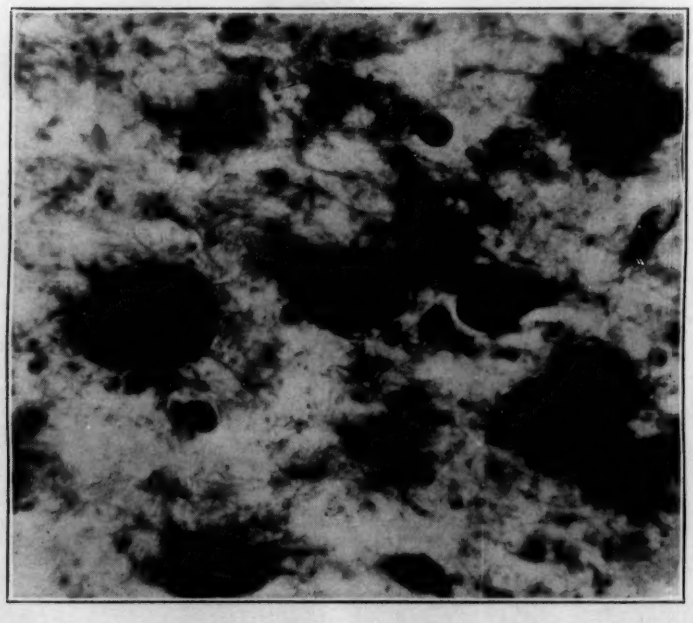

Fig. 4.—Section of cerebral white matter, showing enlarged neuroglia cells resembling gemästete (mast) cells; hematoxylin–eosin stain; × about 750.

The large neuroglia cells consisted of a rather large, irregular, oval nucleus, with distinct chromatin bodies, and a large amount of hyaline protoplasm without granules (fig. 4). They stained only faintly with hematoxylin and took no other stain, neither with the Weigert-Pal nor with the sudan technic.

The vessels were normal; only in the somewhat less affected areas, such as the occipital lobes, a number of fat granule cells surrounded them; in general, such cells were scanty.

In the lateral and ventral thalamic nuclei the ganglion cells were severely degenerated and had almost disappeared. In the medial thalamic nuclei they were scanty and showed severe Nissl degeneration. Degeneration of the ganglion cells was slight in the cerebral cortex, while in the lower gray centers only swelling of the protoplasm was noticeable. In the cord the motor neurons of the anterior horns were severely swollen, the Nissl bodies had disappeared and many of the neurons contained a lump of hyaline matter.

Neither in the membranes nor around the vessels of the brain was there any sign of inflammation.

Comment on the Case.—It is obvious that the clinical and histologic features of this case have much in common with those of cases of infantile diffuse sclerosis as described by de Lange,[1] Krabbe,[2] Greenfield,[3] Eiselsberg[4] and Russel and Tallerman,[5] although in the last two reports the histologic changes were different. Even the peculiar feature of cases of infantile familial sclerosis which was emphasized by van Bogaert and Scholz,[6] that is, the incomplete breaking down of the myelin into prelipoids, which with the Weigert-Pal technic take the same color as the myelin sheaths, was conspicuous in my case.

Further Investigations.—Still during the histologic examination I was reminded of the cases of lead intoxication in infants which I have studied in this country.[7] Encephalopathia saturnina has much in common with diffuse sclerosis and was initially mistaken for it. Therefore in this case I asked Mr. Meuleman, head

1. de Lange, C.: Ueber die familiäre infantile Form der diffusen Gehirnsklerose (Krabbe), Ann. pædiat. **154**:140-179, 1939-1940.

2. Krabbe, K.: A New Infantile, Familial Form of Diffuse Brain Sclerosis, Brain **39**:74-114, 1916; Beiträge zur Kenntnis der Frühstadien der diffusen Hirnsklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **20**:108-115, 1913.

3. Greenfield, J. G.: A Form of Progressive Cerebral Sclerosis in Infants, Associated with Primary Degeneration of the Interfascicular Glia, Proc. Roy. Soc. Med. **26**:690-697, 1933.

4. Eiselsberg, F.: Ueber frühkindliche familiäre diffuse Hirnsklerose, Ztschr. f. Kinderh. **58**:702-725, 1937.

5. Russel, D. S., and Tallerman, K. H.: Familial Progressive Diffuse Cerebral Sclerosis of Infants, Arch. Dis. Childhood **12**:69-86, 1937.

6. van Bogaert, L., and Scholz, W.: Klinischer, genealogischer und pathologisch-anatomischer Beitrag zur Kenntnis der familiären diffusen Sklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **141**:510-541, 1932.

7. Verhaart, W. J. C.: (*a*) Zur Markdegeneration im Gehirn bei Säuglingen, Ztschr. f. d. ges. Neurol. u. Psychiat. **147**:76-91, 1933; (*b*) Encephalopathia Saturnina in Chinese Infants, Far East. A. Trop. Med., Tr. Ninth Cong. **2**:583-592, 1934.

of the chemical laboratory of the pediatric department, to analyze the brain and the liver, and he found them to contain large quantities of lead, 270 and 315 mg., respectively, per kilogram of exsiccated matter.

After the presence of lead was established, a new investigation of the state of health of the other children was undertaken, and it was proved that the siblings were perfectly healthy, and that the child that previously was reported to have died from a disease similar to that of my patient had been ill with high fever for only a week and had never suffered from impaired gait or stiffness of the legs.

Summary of Pathologic Data.—It must be accepted that the child suffered not from infantile diffuse sclerosis (Krabbe) but from a form of chronic lead encephalopathy. The source of the lead could not be determined; the toilet powder contained no lead, the family used tap water and no recently soldered pans were in use. However, the lead may not have entered the body recently. It is known that lead may be deposited in the bones and remain for a long time without doing harm; then some change in the metabolism or in the acid-base balance may mobilize it and lead intoxication may result.

COMMENT

A case of toxic encephalopathy in which the changes were similar to those in cases of familial degenerative diseases is not surprising, since such changes have been experimentally evoked by Ferraro [8] in cats and monkeys by the subcutaneous administration of potassium cyanide. The exact features of such degeneration certainly depend not only on the type but the quantity of toxin given (Lotmar [9]). In adult animals lead intoxication usually causes degeneration of ganglion cells (Ferraro and Hernandez [10]); however, sometimes demyelination is found in young animals; [7b] incomplete myelination and greater activity of the oligodendrocytes in youth may play some role in this difference. The possible role of lead intoxication in other cases of diffuse and multiple sclerosis has already been mentioned by Cone, Russel and Harwood,[11] but the importance of the factor cannot be estimated because lead has not been looked for in all the cases. In this country a diagnosis of diffuse sclerosis in children should not be made until saturnism has been excluded.

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8. Ferraro, A.: Experimental Toxic Encephalomyelopathy: Diffuse Sclerosis Following Subcutaneous Injection of Potassium Cyanide, Arch. Neurol. & Psychiat. **29**:1364-1367 (June) 1933.

9. Lotmar, F.: Zur Wirkung des Dysenterietoxins auf das Zentralnervensystem, Ztschr. f. d. ges. Neurol. u. Psychiat. **8**:345-351, 1912.

10. Ferraro, A., and Hernandez, R.: Lead Poisoning, Psychiatric Quart. **6**: 319-350, 1932.

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HEREDITY OF PSEUDOHYPERTROPHIC MUSCULAR DYSTROPHY

WALTER S. POLACHECK, M.D.
MILWAUKEE

Gowers [1] in 1879 recognized the hereditary nature of pseudohypertrophic muscular dystrophy. He believed that in cases in which the disease developed early in life the disorder was transmitted only through the mother and that in cases in which the disease began in adult life inheritance might be through either parent.

Weitz [2] in 1921 expressed the belief that the inheritance of the disease might take two different forms, being a simple recessive in some families and a sex-linked recessive form in others.

Minkowski and Sidler [3] from study of family records for a two hundred year period in a secluded Swiss village came to the conclusion that the inheritance of the disorder was of the recessive type and that children in whom the disease developed were born only of marriages between members of afflicted families, the recessive character for the disorder necessarily being present in both parents.

There have been many reports and presentations of family trees both in the American and in the foreign literature which show that in some families the disorder is a sex-linked mendelian recessive trait and that the disease appears only in the male descendants of unafflicted female carriers. In this respect it has the same hereditary mechanism as hemophilia.

Koslakow [4] in 1934 presented a genealogic tree for three generations of a family with 47 living members. In 15 of 20 male members the disorder had developed, while 27 female members remained healthy. In all cases the disease, transmitted through healthy female carriers, was a sex-linked mendelian recessive trait.

Similar family trees, illustrating the same type of hereditary mechanism, were published by Voshell [5] in 1933 and by Orbuse and Sloan [6] in 1937.

From the Children's Hospital.

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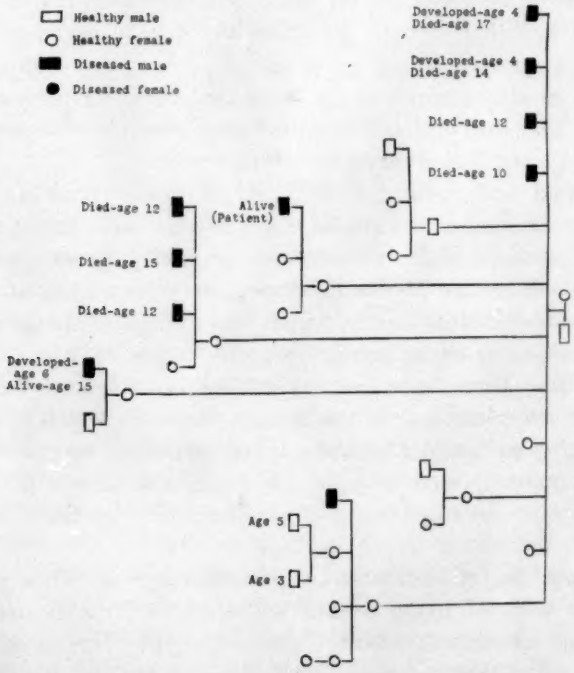
I am presenting a genealogic tree for a family in which 10 male members in three generations have had pseudohypertrophic muscular dystrophy. The disorder is clearly seen to be a sex-linked mendelian recessive trait.

In the boys of the family which I have observed, the onset of the disorder has been gradual beginning sometime between the fourth and the seventh year of life, and the disease has slowly progressed to a fatal termination occurring usually between the ages of 10 and 17 years. The muscles of the persons afflicted were said to have been enlarged at first,



Patient's family tree, illustrating that the character for pseudohypertrophic muscular dystrophy is a sex-linked mendelian recessive transmitted by normal female carriers and that the disease develops in the male offspring.

with a typical pseudohypertrophic appearance, and then to have wasted away in terminal atrophy.

REPORT OF A CASE

The patient, a boy, was born Feb. 24, 1929 after an uneventful labor lasting thirty-two hours. He was breast fed for eight months. His first tooth appeared at 7 months of age, and he learned to walk at 14 months and to talk gradually between the ages of 2½ and 3 years.

The onset of muscular weakness was first noted at the age of 3 years, the first sign of muscular dystrophy being weakness when walking on the toes.

After this there was a gradual onset of generalized muscular involvement. At first the muscles were enlarged and weak, with a pseudohypertrophic appearance. Gradually they atrophied and shrank to below normal size.

At the age of 10 years, on admission to the hospital, where he remained from April 11 to May 2, 1939, generalized muscular atrophy and weakness were present. There was marked deformity of the chest, with anterior-posterior flattening and atrophy of the external muscles. The head seemed excessively large in proportion to the size of the chest. The extremities were thin and wasted. The legs were unable to support the body in the standing position and were useless even for moving the body along the floor. There was foot drop bilaterally. The arms and hands were extremely weak, but the patient could still feed himself, with difficulty.

The routine blood counts and examinations of the urine showed no significant abnormalities.

SUMMARY

A family tree is presented which illustrates that pseudohypertrophic muscular dystrophy is transmitted as a sex-linked mendelian recessive trait by normal female carriers to their male offspring.

SOLITARY EOSINOPHILIC GRANULOMA OF BONE

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The purpose of this communication is to call attention to an unusual form of bone granuloma, 2 examples of which came under my observation in private practice. Both of these cases are being reported by the pathologists who examined the specimens; however, I believe the cases are of enough importance from the standpoint of clinical diagnosis and prognosis to warrant a report with emphasis on the clinical features of the condition.

REPORT OF CASES

CASE 1.—Leonard U., the second of 3 children, was born in May 1930. The birth was normal, and the birth weight was 7 pounds 10 ounces (3,460 Gm.). He was breast fed and progressed well. I first saw him in June 1932, when he was brought to me on account of cough and noisy breathing. He showed definite signs of bronchial asthma. In October 1932 he had a second attack of asthma.

I did not see him again until Sept. 17, 1934, when his mother brought him to me because of a swelling, which she had noted five weeks previously, on the left side of the skull near the frontoparietal suture. The swelling, which was about the size of a walnut, was soft, fluctuating and nontender. There was no local heat or redness and no history of pain; the swelling had come to the mother's notice while she was combing the boy's hair. There was no other feature of importance in the history. There had been no loss of weight; his appetite was good; his color was excellent and he seemed well. There was no history of trauma, nor was there any family history of neoplasm or tuberculosis.

Physical examination revealed a healthy but somewhat small boy. His weight was 32 pounds (14.54 Kg.). Normal weight for his age is 38 pounds (17.27 Kg.). Except that he was short for his age, he seemed entirely normal. The ocular fundi were not unusual. The mass on the skull seemed too soft to be a sebaceous cyst. There were no signs pointing to an abscess. A roentgenogram of the skull showed a circular defect, measuring about 2 by 3 cm., at the site of the swelling (fig. 1 *A* and *B*). Roentgenograms of all the other bones were normal.

Laboratory Data.—The tuberculin and Wassermann reactions were negative. Results of urinalysis were normal. Examination of the blood gave the following results: hemoglobin content, 88 per cent; red cells, 4,810,000; platelets, 410,000; and white cells, 17,000, with 27 per cent segmented polymorphonuclear neutrophils, 2 per cent staff polymorphonuclear neutrophils, 11.5 per cent polymorphonuclear eosinophils, 1 per cent polymorphonuclear basophils, 52 per cent lymphocytes, 6 per cent monocytes and 0.5 per cent plasma cells. The value for cholesterol was 202 mg. per hundred cubic centimeters and for cholesterol esters 122 mg.

Operation.—The boy was hospitalized and was seen by Dr. Ira Cohen, who aspirated material from the mass but made no definite diagnosis. Because of the roentgen observations, a diagnosis of Hand-Schüller-Christian disease was considered, but since there was a possibility that the lesion was a neoplasm, an

operation was performed by Dr. Cohen. A defect in the bone, about the size of a quarter, filled with grumous, yellowish material, was found lying on the dura. The material was removed, the edges of the bone were curetted and the wound was closed. The patient's recovery was uneventful.

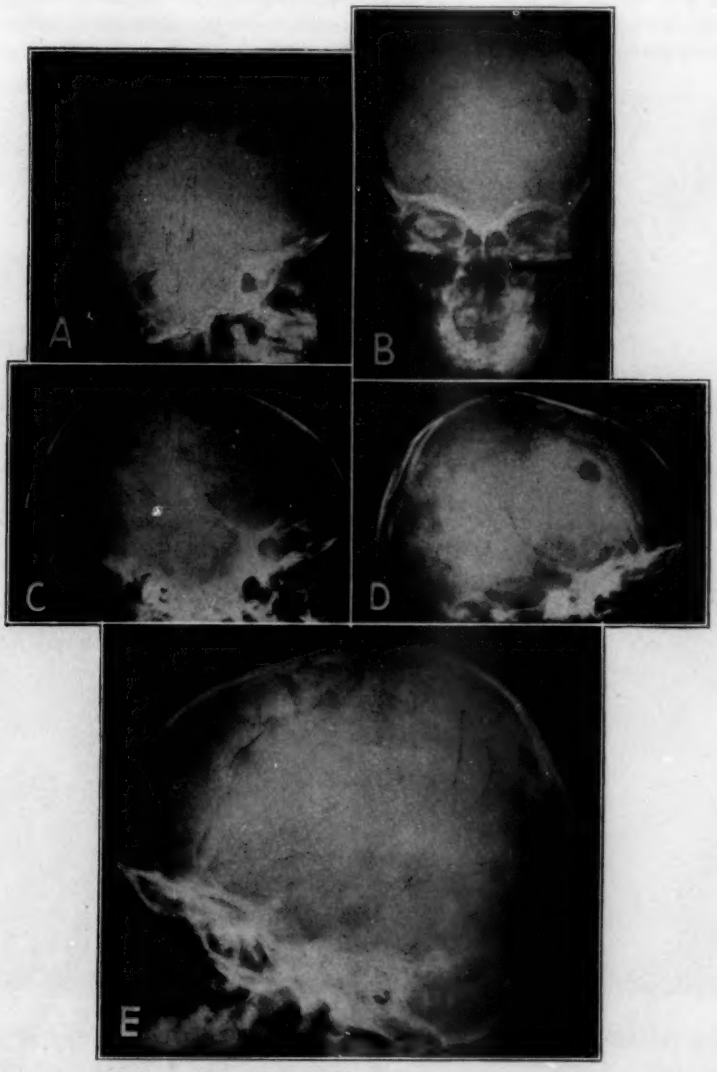

Fig. 1 (case 1).—Roentgenograms of the skull. *A*, lateral, and *B*, antero-posterior, view taken Sept. 22, 1934. *C*, lateral view taken Dec. 29, 1934, after operation. *D*, lateral view taken March 29, 1935, showing healing of the defect. *E*, lateral view taken March 26, 1936, showing that the skull is completely healed.

Course.—Subsequently, five roentgen treatments, totaling 500 r (200 kilovolts, with a 0.25 cm. filter), were given exactly over the site of the lesion. The defect

in the skull gradually filled in, so that the plate taken in March 1936 showed no abnormality (fig. 1 *C*, *D* and *E*).

In the fall of 1935 the boy broke the proximal phalanx of his right index finger. This injury healed perfectly and without difficulty. In 1935 he had a mild attack of poliomyelitis, from which he recovered with no residual paralysis. Since then he has been in excellent health; he is still under my observation. Repeated roentgenograms of the skull and long bones have shown no abnormal structure.

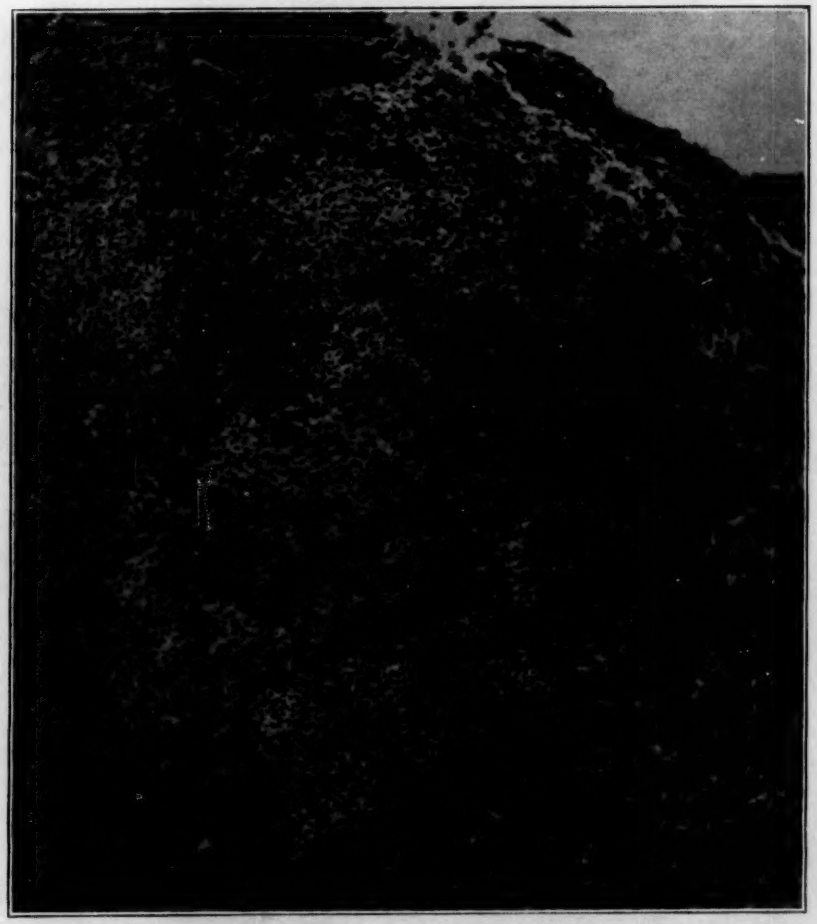

Fig. 2 (case 1).—Section of tissue removed from skull; low magnification.

Histologic Diagnosis.—Examination of the tissue removed at operation gave rise to considerable discussion (figs. 2 and 3). Dr. Paul Klemperer's report was as follows:

"The histologic examination shows a cellular lesion consisting of large polygonal cells, occasional multinuclear giant cells with similar nuclei and an excessive number of mature, eosinophilic leukocytes. There are areas of necrosis, and around these some of the reticulum cells and giant cells contain isotropic fat droplets.

"In making the diagnosis, neoplasm or granuloma must be considered. In view of the predominance of reticulum cells, it is possible that the lesion is a granuloma of the Hand-Schüller-Christian type, although the absence of anisotropic fat must be noted."

The microscopic sections were submitted to Dr. Francis Carter Wood, who agreed that the lesion most resembled that found in Hand-Schüller-Christian disease, the large phagocytic giant cells and the granulation tissue being characteristic. The small amount of fat in the lesion was thought to be due to the fact

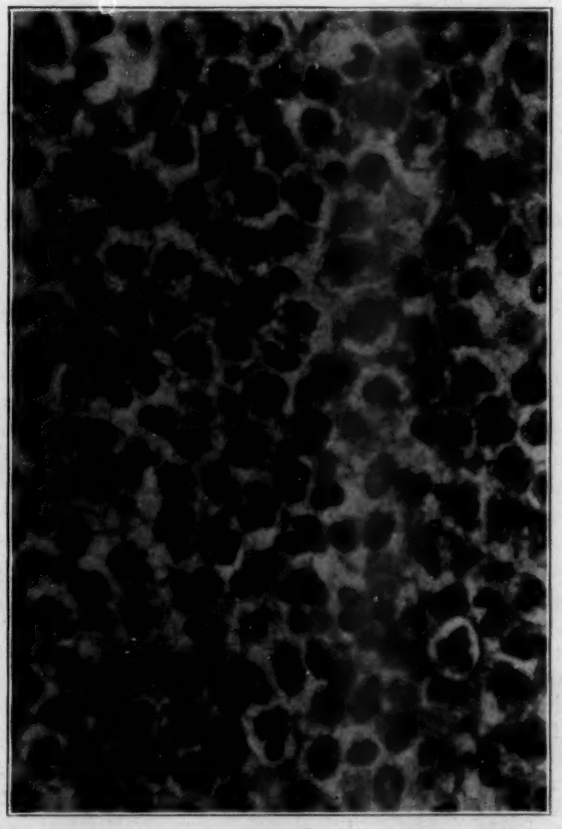

Fig. 3 (case 1).—Section of tissue removed from skull; high magnification.

that the patient was a child and that therefore not as much lipoid was available in the short time that the growth had been present.

A section was also sent to the late Dr. Richard Jaffé, of Chicago, who also expressed the opinion that the disease belonged in the group of granulomas, probably of the Hand-Schüller-Christian variety. He commented on the possibility that the lipoid disturbance was a secondary development, that is, that the lipoid had infiltrated the granulomatous tissue later. According to this view the lipoid disturbance in Hand-Schüller-Christian disease would not be the primary pathologic factor. Dr. Jaffé mentioned a case he had seen, that of a boy with a solitary lesion

in a vertebra, which was reported as an instance of Hand-Schüller-Christian disease, although the biopsy showed reticular cells and great numbers of eosinophilic leukocytes. The patient received roentgen therapy and made a perfect, permanent recovery.

The final diagnosis in my case was granuloma, most probably of the Hand-Schüller-Christian variety.

CASE 2.—Richard B., aged 12 years, has been under my care since his eighth year. He is the second of 2 children and has always been in excellent health. At 8 months of age he had pertussis and at 9 years measles. At the age of 10 years he had a moderately severe attack of lobar pneumonia, which involved the lower lobe of the right lung; since that time he had been well, until the present illness began.

During the summer of 1939, while he was in camp, he began to have pain occasionally over the right side of his chest. This discomfort did not interfere with his activities, but after he left camp and returned to his parents the pain had increased and his side had become tender. Thinking that the condition had a muscular or postural origin, the parents took him to an orthopedist, who examined the chest roentgenographically and found a lesion in the fifth rib on the right side.

On Sept. 5, 1939 he appeared to be in good health. His weight was 84½ pounds (38.4 Kg.), and his height was 57 inches (142.5 cm.). His color was excellent, and the results of a physical examination were normal except for tenderness over the lower part of the right side of his chest in the axillary line. There was definite fulness over this part of the chest, but no heat or redness was observed. Auscultation of the underlying lung gave normal results. The temperature was 100.5 F.

Laboratory Data.—The urine was normal. Examination of the blood gave the following results: hemoglobin content, 88 per cent; red cells, 4,340,000, and white cells, 9,800, with 61 per cent polymorphonuclear neutrophils, 1 per cent polymorphonuclear eosinophils, 36 per cent small lymphocytes, 1 per cent large lymphocytes, and 1 per cent monocytes. The tuberculin and Wassermann reactions were negative.

Roentgen Examination.—Dr. M. Pomeranz reported on the results of a roentgen examination, as follows: "An expansile tumor of the fifth rib on the right side involves the anterior extremity for a distance of about 2 inches (5 cm.). The cortex of the rib anteriorly is perforated at several points. The lesion is somewhat oval and is sharply demarcated. Within the tumor there is some coarse, but not typical, trabeculation. The tumor is almost exclusively osteoclastic, although at its tip there is some bone reaction. The contiguous surface of the sixth rib is somewhat thinned out, either by pressure of the mass or by invasion. Oblique views of this area disclose pleural thickening which involves the axillary border of the lung.

Examination of the chest fails to reveal any evidence of a metastatic process. Roentgenograms of all other bones are normal.

Diagnosis: The lesion of the fifth rib on the right side is a medullary sarcoma (fig. 4).

The roentgenograms were seen by a number of other physicians, all of whom concurred in the diagnosis of a malignant lesion of the bone.

Operation.—The boy was hospitalized and was operated on by Dr. Harold Neuhof. Preoperative irradiation of the mass was done on two successive days, a total of 200 r being given (140 kilovolts, anode-skin distance 50 cm., filter 0.05 mm. of copper and 3 mm. of aluminum, field 10 by 10 cm.). An incision revealed that the anterolateral portion of the fifth rib on the right side was the seat of a tumor which involved not only the rib itself but the underlying parietal pleura.

Examination of a frozen section of the tumor led to no absolutely definite diagnosis, and the entire mass, including the rib and the involved portion of the pleura, was excised.

The patient had a rather stormy postoperative course. Serous pleurisy developed, and the pneumothorax disappeared slowly. However, after six weeks the lung had completely expanded, and he made an excellent recovery. He has remained in very good health since (ten months).

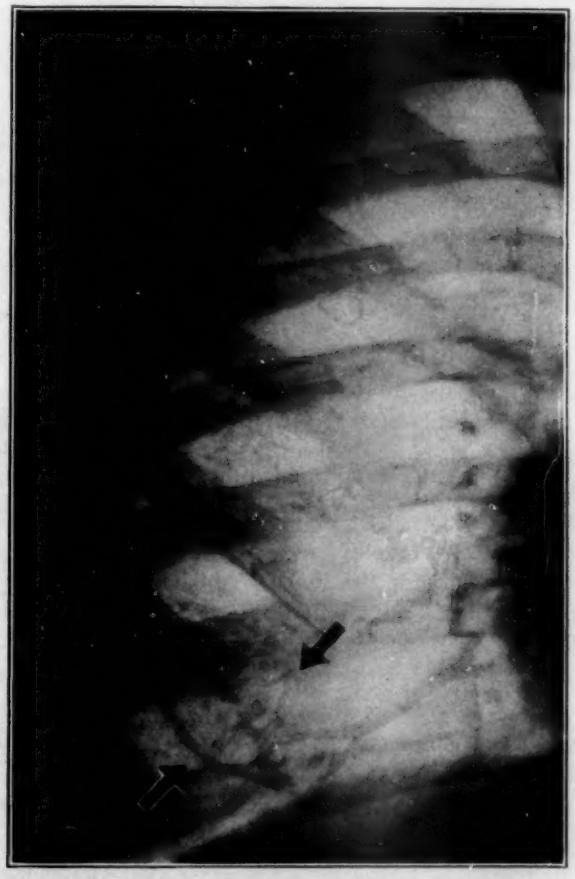

Fig. 4 (case 2).—Roentgenogram of the right side of the chest, showing the lesion in the fifth rib.

Pathologic Examinations.—Dr. Henry L. Jaffe, of New York, gave the following report: "Examination of the specimen of resected rib showed that at a point about 1½ inches (3.8 cm.) lateral to the costochondral junction the lesion had expanded the rib and perforated the cortex and was extending into the neighboring soft tissue. Sagittal section of the specimen showed that the medullary cavity of the rib for about 4 inches (10 cm.) lateral to the costochondral junction was occupied by rather yellowish gray, dense, nonosseous tissue, which was invading the cortex and had perforated it in one region.

Microscopic examination of the tissue occupying the medullary cavity showed it was composed of a substratum of fairly large cells with pale nuclei. Some of these cells had two or three nuclei and were large and distinctly of the giant cell type. This supporting tissue was heavily infiltrated with polymorphonuclear leukocytes, but nowhere could one see abscess formation or other indications of an acute suppurative infection. The majority of the polymorphonuclear leukocytes permeating the tissue were eosinophilic.

One can definitely rule out all the usual types of malignant bone tumors, including Ewing's tumor and spindle cell, or osteogenic, sarcoma. Certain features of the lesion suggest that it is some sort of granuloma, but it does not fit into any of the well known categories of granulomas.

COMMENT

In 1938 Schairer[1] described the cases of 2 boys, 1 of whom was 9 years old and the other 10. In both there appeared a solitary swelling of the skull which was soft and was neither hot nor tender. There was no fever. A roentgenogram in each case showed a circular defect in the bone. No other bones were involved. A malignant tumor was suspected, and the diseased tissue was excised. The dura was thickened, and the tumor tissue was adherent to it. Microscopically the sections showed connective tissue, eosinophilic leukocytes and large cells with pale nuclei (fibroblasts or reticulum cells). In the diagnosis the author considered myeloid leukemia, Schüller-Christian disease and osteodystrophia fibrosa (Recklinghausen's disease). However, the observations did not seem to fit any of these exactly. Both patients made complete recoveries. One had an eosinophil count of 8 per cent.

Schairer commented on the similarity of these 2 cases: in both there were symptomless swellings of the scalp and underlying defects in the skull filled with soft granuloma-like tissue in which eosinophil cells and deposits of hemosiderin predominated. He stated that though trauma may play a role, the cause of the condition is unknown.

Schairer's cases and my case appear to be examples of the same disease. The clinical histories in the 3 cases were similar. The lesions were solitary, they were located in the skull and they were unaccompanied by general symptoms; the number of eosinophils in the peripheral blood was increased, and the pathologic tissue removed at operation was similar. My case 2 is apparently another example of the same disease process, though the lesion was in another bone, a rib.

In each of the 2 cases I have described a single bone lesion was present. In 1 case it was painless, and in the other the region involved was tender and painful. In both cases the lesion both clinically and roentgenologically appeared to be a neoplasm. Both patients were operated on, and the type of tissue found in the lesion was similar in

1. Schairer, E.: Ueber eine eigenartige Erkrankung des kindlichen Schädels (Osteomyelitis mit eosinophiler Reaktion), Zentralbl. f. allg. Path. u. path. Anat. **71**:113 (Nov. 22) 1938.

the two cases. After wide excision roentgen treatment was given, and both patients made perfect recoveries. The patient in case 1 has been in excellent health for almost six years since operation, and the patient in case 2 has been well for almost one year.

Dr. Henry L. Jaffe, who saw the patient in case 2 with me and examined the pathologic material, made brief mention of this case and of another which he and his associate Dr. Louis Lichtenstein had previously observed and which they reported in a paper under the title of "Eosinophilic Granuloma of Bone."[2] The case was that of a 4 year old girl whose chief complaint was pain in the left thigh. Roentgenograms revealed a lesion in the upper third of the femur, which was interpreted as a tumor. The preoperative diagnosis was not certain, but osteomyelitis, tuberculous osteitis and Ewing's tumor were considered. At operation the periosteum over the shaft of the femur just below the trochanter was found congested and the femoral cortex thinned. The authors stated: "A cortical window was removed, exposing a cavity in the bone containing approximately 10—15 cc. of blood-tinged fluid and lined by a soft yellowish tissue which was thoroughly curetted." Cultures of material taken from the operative field were sterile. The material obtained from the diseased bone proved to be granulomatous tissue infiltrated with large masses of eosinophilic polymorphonuclear leukocytes, scattered between which were formations described as "compacted, tumor-like aggregates of cells of fairly uniform type, with large, pale, oval or kidney shaped nuclei." The authors concluded that the lesion represented "a peculiar granuloma of bone of undetermined etiology (possibly a virus granuloma)."

In addition to their own observations and those of Schairer, previously mentioned, these authors called attention to 2 other cases in the literature. Finzi,[3] in 1929, reported the case of a boy of 15 years in which a similar solitary lesion in the frontal bone was described as "a myeloma with prevalence of eosinophil cells," Mignon[4] reported the occurrence of a similar solitary lesion in the frontal bone of a boy aged 12 years.

Otani and Ehrlich[5] reported 3 cases besides my case 2, the pathologic material of which they also studied.

From the data so far given it is evident that my case 1 is not an example of Hand-Schüller-Christian disease but that it and case 2

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2. Lichtenstein, L., and Jaffe, H. L.: Eosinophilic Granuloma of Bone, Am. J. Path. **16**:595 (Sept.) 1940.

3. Finzi, O.: Mieloma con prevalenza delle cellule eosinofile, circoscritto all' osso frontale in un giovane di 15 anni, Minerva med. (pt. 1) **9**:239 (Feb. 17) 1929.

4. Mignon, F.: Ein Granulationstumor des Stirnbeins, Fortschr. a. d. Geb. d. Röntgenstrahlen **42**:749 (Dec.) 1930.

5. Otani, S., and Ehrlich, J. C.: Solitary Granuloma of Bone, Am. J. Path. **16**:479 (July) 1940.

belong in this new class of eosinophilic granulomas. Cases of solitary lesions of bone xanthomatosis, some of which appear in the literature under the title of Hand-Schüller-Christian disease, must be restudied; some of them may well fall into this new category. The disease, represented by these cases, is characterized by the rapid appearance of a swelling, most often in the skull but sometimes in a rib or a long bone, which may or may not be painful or tender. The mass may increase rapidly in size. The overlying skin is not affected, and there are no severe general symptoms, though low grade fever may be present (case 2). Considerable increase in eosinophils may occur (case 1, 11.5 per cent; Schairer's second case, 8 per cent; Lichtenstein and Jaffe's case, 4 per cent; Finzi's case, 10 per cent, and Mignon's case "moderate"). The process apparently starts in the medulla and causes an expanding lesion of the bone which leads to perforation of the cortex, made evident clinically by definite swelling. It is a disease of childhood or early adult life, and most of the cases of the disorder have occurred in males.

The recognition of this clinical picture is important, because the rapid progression of the symptoms and particularly the roentgenographic appearance are characteristic of a malignant growth. The condition must be differentiated from malignant tumors, solitary myeloma, solitary lesion of xanthomatosis (Hand-Schüller-Christian disease), bone cysts and the osseous lesions of leukemia and Hodgkin's disease. Although, as pointed out by Lichtenstein and Jaffe, a preoperative diagnosis may be suspected when a child or young adult has a solitary expansile bone lesion, especially if it is located in the calvarium, which is perhaps accompanied by a moderate degree of eosinophilia and is not associated with general symptoms of illness, the diagnosis can be verified only by operation and by examination of excised tissue. Treatment consists in wide excision of the diseased area and subsequent roentgen therapy. The prognosis for patients thus treated is excellent. The lesion apparently does not recur locally, nor have any secondary lesions elsewhere in the body been described.

SUMMARY

Two cases of an unusual type of solitary eosinophilic granuloma of bone occurring in childhood have been described. This condition, of which 8 other cases have been reported in the literature, is apparently a distinct disease entity. Roentgenologically it fulfils all the criteria of malignant disease of bone. It is important to know of this condition, since though clinically and roentgenologically it closely resembles malignant disease, it is benign and by operation and irradiation the patient may be permanently cured.

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CONGENITAL STENOSIS OF THE TRACHEA

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Congenital stenosis of the trachea is one of the most unusual anomalies of the respiratory tract. The lesion receives meager comment or no mention at all in the well known textbooks of otolaryngology and pediatrics, and the number of cases on record is small.

REPORT OF A CASE

History.—On Feb. 17, 1938 a two month old white girl was admitted to the Children's Hospital of Philadelphia, where she died after eleven days. Gestation had lasted approximately eight and a half months; the delivery had been spontaneous and the labor brief. Her parents were young and the patient was their first child. The baby weighed only 4 pounds 10 ounces (2,098 Gm.) at birth. She was fed an evaporated milk formula and her appetite and elimination had always been good.

Since birth she had appeared feeble and puny, and when she cried, which was seldom, she gave a faint, weak cry. At 4 weeks of age she had a mild cold in the head which lasted a few days; during this illness no peculiarities in breathing were noted.

When she was 6 weeks of age she suddenly collapsed and became cyanotic, breathing became labored and suckling difficult. She was admitted to one of the local hospitals; she was observed for one week, during which time she had a number of similar attacks. Roentgen irradiation of the thymus produced no improvement. The child was then transferred to the Children's Hospital.

Physical Examination.—On admission the baby was noted to be undernourished and immature. Her skin was pale and mottled, and the mucous membranes were faintly cyanotic. The respirations, which numbered 30 per minute, were labored and stridorous and had an expiratory wheeze. She weighed 6½ pounds (2,948 Gm.); the temperature was 98 F. and the pulse rate 168 per minute. There was superficial eczematous scaling of the skin of the face, the anterior portion of the chest and the postauricular creases. Numerous sibilant rales were audible in all parts of the chest, though most abundant at the base of the left lung. The breath sounds were louder on the right side. On percussion the mediastinal and cardiac dulness extended unusually far to the right but was normal on the left. The heart sounds were regular, and there were no murmurs. The abdominal organs were not palpable. Results of a neurologic examination were not significant.

Laboratory Data.—The results of blood counts and urinalyses were normal, and the Wassermann and Kahn reactions were negative. The blood calcium was 9.8 mg.

Read before the Section on Otolaryngology, American College of Surgeons, Oct. 20, 1939.

From the Children's Hospital and the Department of Pediatrics, University of Pennsylvania School of Medicine.

and the blood phosphorus 6.7 mg. per hundred cubic centimeters. The reaction to a Mantoux test (0.01 mg. of old tuberculin) was negative.

Roentgen Examination.—The reports of the roentgen examinations (Dr. R. S. Bromer) were as follows: Feb. 18, 1938 (fig. 1): "The mediastinal and cardiac shadows show increased width on the right side, as though retraction of the heart to the right were present. The possibility of atelectasis of the inner portion of the upper lobe of the right lung cannot be excluded. The stomach lies on the left side and the liver on the right. Except for the density in the upper lobe of the right lung, the lungs are clear. In the lateral view the trachea appears narrow throughout its length."

February 24: "No changes have occurred in the right side of the chest since the last examination. The oblique films show no evidence of mediastinal involvement or any pathologic process hidden by the cardiac shadow."

February 26: "The long bones show no evidence of syphilis or of other pathologic changes."

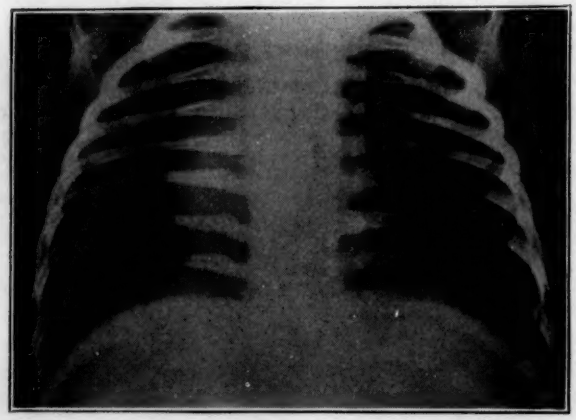

Fig. 1.—Roentgenogram of the chest taken ten days before death. The shadows of the mediastinum and the heart show increased width on the right side. The left border of the heart seems displaced to the right. The necropsy revealed complete atelectasis of the upper lobe of the right lung, secondary to bronchial occlusion.

Electrocardiographic Examination.—An electrocardiogram made on February 24 demonstrated a regular cardiac rhythm of 188 per minute, with a sharp P wave in lead II and a PR interval of 0.10 per second. The QRS complexes were of low voltage and were splintered in leads II and III. There was moderate right axis deviation.

Course.—The baby had numerous spasmodic attacks of respiratory wheezing, during which she would become too feeble to cry and her face would take on an ashy gray pallor, most striking about the lips. Day by day her respirations became steadily more noisy and stridorous. She nursed poorly, showed occasional rises of body temperature to 100 F. and gained only a few ounces in weight. Two injections of calcium gluconate (10 cc. of a 10 per cent solution given intramuscularly) had no beneficial effect.

On February 26 the ear drums, which previously had been normal, began to show catarrhal inflammation and the nasal turbinates became congested, swollen and coated with mucopus. The respirations grew more rapid and became labored and stridorous. The infant appeared profoundly ill. Neither a transfusion of 50 cc. of citrated blood nor administrations of epinephrine and atropine gave relief. Slight temporary benefit was obtained from placing her in an oxygen tent.

Tracheotomy was attempted on February 27 because of an increasing expiratory wheeze, with sternal indrawing and other evidences of obstructive dyspnea. The incisions into the tissues of the neck and the trachea were readily carried out, but the trachea was too narrow to admit the smallest available tracheotomy tube, size 0. This finding of contracted tracheal lumen suggested to the surgeon, Dr. E. H. Campbell, the presence of congenital stenosis. A small rectangular window was cut out of the upper three cartilages and a large-sized rubber tube sewed into position, with one end over the window and the other extending outward through the wound in the neck. It was possible to aspirate small quantities of mucous by introducing a small suction tube through this large tube. Some easing of the breathlessness was obtained thereby, but the general condition of the baby did not appear improved by the operation.

The infant was placed in a closed incubator chamber of the Chapple type and given a mixture of 50 per cent helium and 50 per cent oxygen to breathe. Marked alleviation of the dyspnea ensued promptly, and the baby ceased gasping and fell quietly asleep, although slight evidences of dyspnea still persisted. Eight hours later she died suddenly while asleep.

Clinical Diagnosis.—The final clinical diagnosis was: prematurity; bronchial asthma (?); bronchopneumonia, bilateral; atelectasis (?); malformation of the trachea (?); sinusitis; catarrhal otitis, and infantile eczema.

Necropsy.—The body, which was undernourished but normally formed, weighed 6½ pounds (2,948 Gm.). A gaping fresh tracheotomy incision was present. The underlying soft tissues were edematous and congested. From the incision an early abscess cavity dissected downward on the right side of the trachea into the upper portion of the mediastinum. An abundance of fibrous tissue was present also, possibly consequent to the roentgen treatments which had been given. No cysts or other obstructive formations were uncovered.

Within the thoracic cavity there was no excess of fluid, adhesions or exudate. The organs lay in their customary positions. The thymus was small, weighing less than 5 Gm. The heart was normally formed and not hypertrophied; its surface was sprinkled with petechiae. The esophagus showed no changes.

The lungs were congested and edematous, particularly in their posterior dependent portions. Each weighed 30 Gm. A few petechiae were scattered over their apexes. There were no areas of pneumonia or of abscess formation. The upper lobe of the right lung was completely collapsed and airless. Patches of lobular atelectasis were scattered through the other lobes of both lungs.

The anteroposterior dimension of the larynx was 8 mm., a figure within the normal range for a child of this age.[1] The vocal cords and the epiglottis were not inflamed or edematous. From the cricoid cartilage, where its diameter was 4 mm., the trachea tapered progressively downward until at its bifurcation it measured

1. Tucker, G.: The Infant Larynx: Direct Laryngoscopic Observations, J. A. M. A. **99**:1899 (Dec. 3) 1932.

only 1.5 mm.[2] The membranous portion of the tracheal wall was absent, and the posterior aspect was as rigid as the remainder of the wall (fig. 2). There were thirty tracheal rings, which appeared unusually narrow and complete and were regularly spaced and formed except for a few cartilaginous plates of bizarre shape at the bifurcation. There was an oblique groove caused by the left pulmonary vein on the posterior tracheal surface above the bifurcation.

The major bronchial branches possessed the normal pattern of subdivision except for being unusually narrow. The main bronchi on cross section each measured 1.5 mm. Their flattened lumens contained mucopurulent secretion, and their mucous linings were injected though not ulcerated. No foreign bodies were found. Further into the hilar region the bronchi were not unduly small and did not appear thickened.

Fig. 2.—Photograph of the posterior aspect of the trachea, showing the progressive narrowing of its lower segment, with complete absence of the membranous portion of the wall.

The abdominal organs lay in their customary anatomic positions and were free from lesions.

Microscopic Examination.—The larynx showed no changes except catarrhal inflammation of the submucosal tissue.

The histologic character of the trachea and its cartilages and other components was normal (fig. 3). The tracheal submucosa was edematous and infiltrated with phagocytes of various sorts. Its epithelium was not missing or metaplastic.

2. The diameter of the normal trachea of a child of the same age as the patient, measured for comparison, was 7 mm. throughout, and the major bronchial branches were each 5 mm. in diameter (fig. 3).

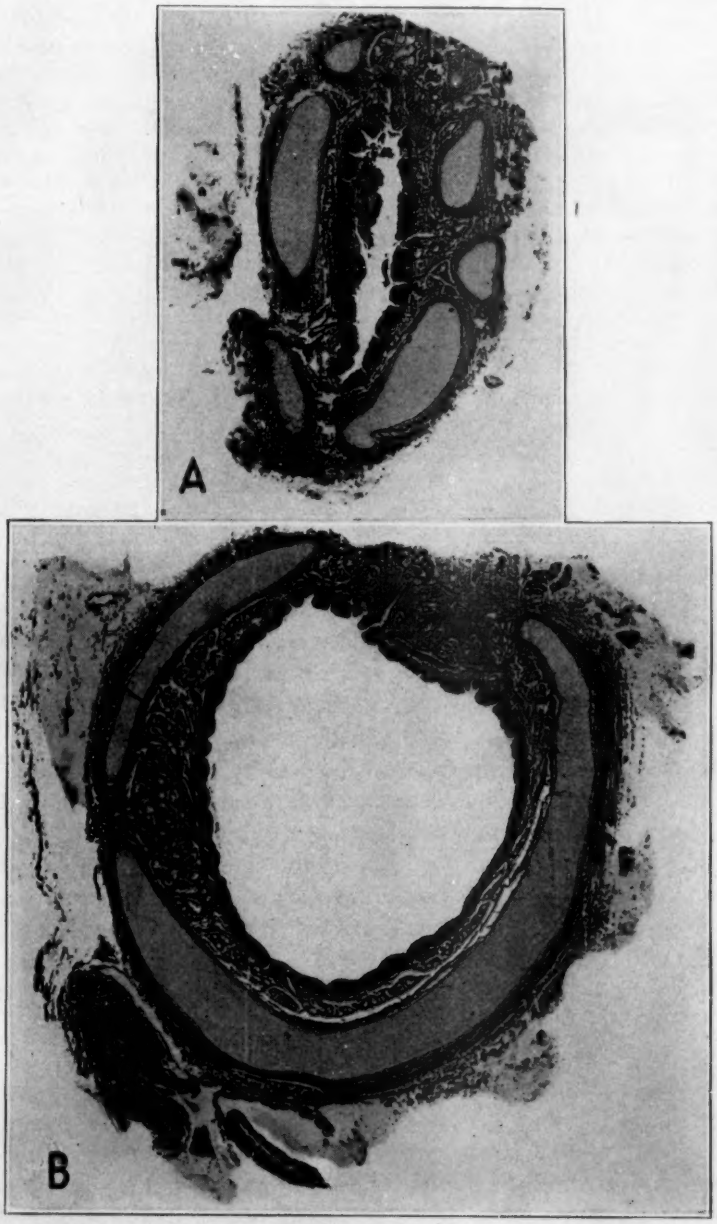

Fig. 3.—Photomicrographs (× 17) of the congenitally stenosed trachea (*A*) and a full-sized trachea from a normal child of the same age (*B*). Note the constricted lumen with a fragment of mucopurulent exudate and the catarrhal inflammatory swelling of the tracheal mucous membrane.

In the major bronchi the inflammatory reaction was similar to that of the trachea, though more advanced and extensive, and mucopurulent discharge was being excreted into their lumens. Extensive cellular infiltration of the submucosa and of the connective tissue surrounding the secretory glands had taken place. The cartilages and epithelium were histologically normal.

Within the lungs the small bronchi and the bronchioles were all partially collapsed but not abnormally narrow or anomalously formed. Their linings showed acute inflammation, which was less marked in the terminal bronchioles. In the upper lobe of the right lung many lobules were collapsed, with involvement of both the alveoli and the bronchioles. Some edema fluid and occasional extravasated red cells were present. There were no evidences of organization. The larger blood vessels were dilated, and the alveolar capillary network stood out prominently. In appearance the upper lobe (of the left lung) resembled that of the other side except that the collapse was not complete. The quantity of edema fluid was greater here, and numerous vacuolated monocytes were seen within the alveoli. On frozen section no fat-containing cells and no abnormal lipoid deposits were found within the lungs.

No pathologic changes except circulatory congestion were noted in the liver, spleen, adrenals, kidneys or myocardium.

Pathologic Diagnosis.—The pathologic diagnosis was: congenital stenosis of the trachea and major bronchi; malformation of the tracheal cartilages; acute catarrhal tracheobronchitis; pulmonary atelectasis; infection of the tracheotomy wound; prematurity and undernutrition.

COMMENT

Search of the literature revealed a few other cases of congenital tracheal stenosis in infants and children, which are listed in the table. Only cases in which the primary malformation occurred within the annular cartilages themselves are included. Cases of stenosis secondary to pressure from organs external to the trachea, such as a constricting double aortic arch,[3] are not included.

In several instances the disturbance was restricted to a short segment 1 to 2 cm. in length, the remainder of the tracheobronchial tree being normally formed. This variety of anomaly is illustrated in *A* of figure 4. On the other hand, the trachea throughout its length and at times the major bronchi as well may be narrowed (fig. 4*B*). In this variety the lumen tapers down from the larynx, becoming no larger than the lead of a lead pencil, as in Finkelstein's case, or less than 2 mm. in diameter, as in the present case. In some of the specimens dissection revealed an increase in the number of tracheal cartilages over the customary eighteen to twenty. Absence of the membranous part of the wall was occasionally recorded.

Several features of the present case merit special emphasis. The child's stridor and dyspnea were clinically puzzling in that they occurred sporadically at first and only later became continuous. The mediastinal displacement had been a baffling diagnostic problem, not elucidated until the atelectasis of the upper lobe of the right lung was disclosed

3. Wolman, I. J.: J. Pediat. **14**:527, 1939.

Data in Cases of Congenital Tracheal Stenosis in Children

Author	Clinical Symptoms	Special Therapy	Age at Death	Pathologic Observations		Type * of Tracheal Lesion
				Trachea	Elsewhere	
Rahn-Eichers, 1832, cited by Denker, A., and Kahler, O.: Handbuch der Hals-Nasen-Ohrenheilkunde, Berlin, Julius Springer, 1926, vol. 2, p. 431.	.....	.....	5 mo.	Narrow throughout	.....	B
Gruber, W.: Oesterr. Ztschr. f. prakt. Heilk. **16**: 7, 1870; cited by Haardt.	.....	.....	Stillborn	Funnel shaped, with 30 cartilages, narrowed to bifurcation; membranous portion absent from cartilages 9 to 25	Aplasia of right lung; no lobes in left lung	B
Schmidt, M.: Deutsche med. Wchnschr. **12**: 608, 1886.	Dyspnea and stridor since birth; no feeding difficulties; occasional attacks of cyanosis	Tracheotomy gave no relief; child died on following day	6 mo.	Congenital lack of rigidity of the normal-sized cartilages; lumen collapsed and kinked	.....	B
Gregor, K.: Jahrb. f. Kinderh. **49**: 123, 1899.	Sporadic attacks of dyspnea; fatigue during feeding	Tracheotomy; tube encountered obstruction in lower part of trachea	5 Mo.	Central portion for distance of 1.5 cm. showed hourglass narrowing; membranous portion absent from cartilages 8 to 15	Bronchopneumonia	A
Moussons, M.: J. de méd. de Bordeaux **37**: 105, 1907.	Continuous stridor and dyspnea since birth; malnutrition; difficulty in feeding	Fed by gavage	3 mo.	One cm. of central portion was narrowed and kinked, with cartilages shrunken, distorted and fragmented	Marasmus	A
Finkelstein, H.: Lehrbuch der Säuglingskrankheiten, ed. 3, Berlin, Julius Springer, 1924, p. 621.	Chronic dyspnea, with continual stridor and cyanosis	.....	4 days	Lumen the size of a pencil lead	.....	B
Guisez, J.: Bull. d'oto-rhino-laryng. **23**: 289, 1927.	Nocturnal attacks of dyspnea from birth until 7 years of age	Dilation with bougies improved respirations, but several hours later severe dyspnea necessitated immediate tracheotomy, with prompt disappearance of symptoms	Survived	Relaxed; upper portion showed hernial dilatation; rigid stenosis in middle portion	Clubfoot	A
Gabriel, E., and Feyrter, F.: Jahrb. f. Kinderh. **121**: 29, 1928.	Stridor after birth, which soon disappeared; breast feeding difficult	Laryngoscopic examination negative; tracheotomy unsuccessful because even smallest tube (size 00, diam. 4.5 mm.) failed to pass	5 mo.	Narrow throughout; membranous portion absent; cartilages 24 and 25 fused and irregular	Malformed brain; diphtheritic laryngotracheitis	B
Lerro, E.: Pediatria **43**: 440, 1935.	Inspiratory stridor since birth; feeding difficulties; gain in weight slow	.....	17 mo.	3 mm. in diameter	Stenosis in lower part of intestine	B
Haardt, W.: Wien. klin. Wchnschr. **51**: 657, 1938.	Dyspnea since birth; occasional attacks of cyanosis; stenosis of lower part of trachea shown in roentgenograms	Exacerbations relieved by knee-elbow position	13 mo.	Upper half normal; lower half narrowed gradually, with lumen smallest just above bifurcation; membranous portion absent in lower half; bifurcation and major bronchi normal	Congenital absence of both thumbs; Meckel's diverticulum; abnormal lobulation of liver	B
Wolman, 1941.	Paroxysms of stridor and dyspnea, growing progressively more frequent	Tracheotomy unsuccessful; atmosphere of 50% oxygen and 50% helium gave marked relief before death	10 wks.	Funnel shaped, with 30 cartilages; constriction narrowest at bifurcation; membranous portion absent; main bronchi stenosed	Prematurity; bronchopneumonia	B

* A and B refer to the types of tracheal lesion illustrated in *A* and *B* of figure 4.

at necropsy. The failure to improve after the irradiation of the thymus was not surprising. Not until the operation on the last day of life, when an extremely slender tracheotomy cannula proved too large for entry, did the first indication of the true character of the ailment become apparent. Death was due to terminal asphyxia secondary to catarrh of the respiratory tract. The mucopurulent secretion, tenacious though scanty, with the inflammatory edema of the mucous membranes completely occluded the major bronchi and the lower part of the trachea. Although the histologic picture is that of bacterial inflammation, it is possible that there may have been an allergic component, since the lesions on the face and trunk resembled those of allergic eczema.

There were no striking new or distinctive symptoms in this case which would render clinical recognition of the lesion less difficult in the future.

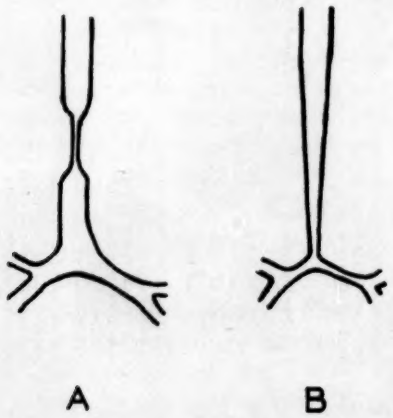

Fig. 4.—Schematic representation of the two most common types of tracheal stenosis. In *A* the constriction is limited to a short segment of the trachea; in *B* the constriction is widespread and most marked at or above the bifurcation.

Wheezing, breathlessness and atelectasis accompany most kinds of tracheal obstruction, whether it is inflammatory, neoplastic or congenital in origin or is brought about by foreign bodies or other causes. Attacks of what might be termed "respiratory failure," with collapse, can be associated with a wide variety of disturbances of the respiratory tract, such as positive pressure pneumothorax and expanding cystic cavities within the lungs.

Visualization by means of the bronchoscope appears to be the only positive means of confirming the diagnosis. Introduction of iodized oil should be avoided in patients suspected of having the lesion because of the possibility of plugging the airway entirely.

In the lateral roentgenogram normal infants often seem to have a narrowing such as was described in the present case unless the picture

is taken during the inspiratory phase of the respiratory cycle. Pressure of the thymus, according to Pancoast and Pendergrass,[4] gives rise to narrowing or buckling of the upper part of the trachea and not of the lower segment.

Whenever a baby manifests obstructive symptoms dating from birth without displaying any lesions which might produce them, such as laryngeal relaxation, inflammatory edema, intrathoracic tumor or aspirated foreign body, the possibility of congenital tracheal stenosis must be thought of.

Evidently the lesion is not always fatal, since a few stenoses which did not produce symptoms have been encountered in autopsies on adults.[5] As the infant grows up the trachea grows too, so that ultimately an airway adequate for normal functioning becomes established. The prognosis is not hopeless.

When the diagnosis is recognized early in infancy the clinician and parents should make every effort to carry the child along until growth relieves the obstruction. Infections of the respiratory tract should be especially guarded against. Experience in the case being reported shows that symptomatic relief of respiratory distress can be obtained by placing the infant within a closed chamber in an atmosphere enriched with oxygen and, if available, helium.

SUMMARY

A case of congenital stenosis of the trachea in an infant is presented. Clinical recognition of the condition is difficult. The possibility of this rare anomaly should be kept in mind in the presence of symptoms of continuous or intermittent stridor with respiratory obstruction for which none of the usual causes can be established.

4. Pancoast, H. K., and Pendergrass, E. P.: Am. J. Roentgenol. **23**:241, 1930.

5. Fleischmann, G.: De vitiis congenitis thoracem et abdomen, Dissert., Erlangen, A. E. Junge, 1820; cited by Denker, A., and Kahler, O.: Handbuch der Hals-Nasen-Ohrenheilkunde, Berlin, Julius Springer, 1926, vol. 2, p. 431. Sankott, A. M.: Wien. klin. Wchnschr. **35**:391, 1922.

BRANCHIOGENOUS CARCINOMA IN A CHILD

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Carcinoma of the neck arising from persistent branchial remnants was first described by Volkmann [1] in 1882. Since that time several hundred cases have been reported, so that the condition is no longer considered more than unusual. Thus in recent years Oliver [2] has reviewed 80 cases from Baltimore, and Crile and Kearns,[3] 28 cases from Cleveland.

In regard to age incidence, there are few malignant growths more strictly confined to adult life than those of branchial origin. Of the 28 patients whose cases were reported by Crile and Kearns, the youngest was 37 years of age. Of the 80 patients whose cases were reported by Oliver, only 3 were younger than 30 years; indeed, he reported the case of the youngest patient of whom I find a record in the literature, a person aged 23 years. It appears to be of distinct interest, therefore, to report a case of branchiogenous carcinoma in a child of 7 years.

REPORT OF CASE

Donald D., a boy aged 7 years, was examined May 19, 1938. There was a swelling of the left side of his neck, first noticed six months previously and noticeably increasing in size from month to month. The mass was about the size of a small walnut. It lay immediately below the left ear, as if wedged between the mastoid and the mandible. It was not tender, and no regional glands were palpable. The mass itself was not movable, but the skin over it was. A roentgenogram showed no calcification. A small dose of radiation produced no reduction in size. All other tests yielding negative or inconclusive results, it was decided that the most likely diagnosis was a branchial cyst.

The mass was removed July 7, 1938. Sharp dissection was necessary throughout because of the adherence of the mass to surrounding structures, apparently by fibrosis of the capsule. It appeared to be multilocular and on accidental rupture exuded amber mucoid fluid. Removal was otherwise uneventful, the wound was closed without drainage, and healing occurred uneventfully.

1. Volkmann, R.: Das tiefe branchiogene Halskarcinom, Centralbl. f. Chir. **9**:49, 1882.

2. Oliver, R. L.: Malignant Epithelial Tumors of the Neck, Am. J. Cancer **23**:16 (Jan.) 1935.

3. Crile, G., and Kearns, J. E., Jr.: Branchial Carcinoma, Surg., Gynec. & Obst. **60**:703 (March) 1935.

Fig. 1.—Donald D., aged 10 years. Branchiogenic cyst on the left side of the neck removed two and one-half years ago, at the age of 7 years. Examination revealed grade 2 epidermoid carcinoma.

Fig. 2.—Branchiogenous carcinoma. Section through the branchial cyst wall shows a moderately well differentiated stratified squamous epithelium with relatively numerous mitoses. The surrounding stroma contains large numbers of round cells and macrophages.

The pathologic examination, by Dr. Paul Michael, of Peralta Hospital, was reported as follows: The microscopic sections showed the cyst wall to present a rather complex structure. In the outer peripheral margins were small areas of mixed mucous and serous glands, derived from the parotid gland. Beneath this was a zone of compressed round cells and some lymphoid follicles. The stroma itself was essentially fibrous tissue with areas undergoing hyaline degeneration. Extending from the middle zone out to the inner lining of the cyst were somewhat distorted immature epithelial cells. In a few places the inner lining was a normal-appearing stratified squamous epithelium, but in several places it showed a fairly distinct increased growth, with large sheets and islands of moderately immature stratified squamous epithelial cells. The latter showed characteristic intercellular bridges, and there were a few scattered mitoses. So far as could be determined from the study of these sections, the tumor appeared to be contained within the cyst.

The pathologic diagnosis was inclusion cyst derived from the second branchial cleft, showing epidermoid carcinoma, grade 2.

After healing of the wound, radiation was administered locally, and the treatment was repeated after one year. The child was last seen Feb. 6, 1941, two and one-half years after operation. There was no evidence of recurrence, and the child was in excellent health.

COMMENT

The internal depressions between the gill arches that appear in the neck in early embryonic life are designated as pouches; the external indentations are known as clefts. The pouches are lined with entoderm; the clefts, with ectoderm. As the mesodermal layer becomes attenuated between these opposing layers, they fuse to form a membrane. Instead of rupturing to form true gills, however, the mesoderm then grows in between the layers, making space for muscles, blood vessels and other structures and largely effacing the original pregill evidence of phylogeny.

Tumors such as the one here reported are generally thought to arise from the second branchial cleft. The second pouch becomes the tonsillar fossa, and the cleft normally disappears. Cysts and tumors arise through persistence as inclusions of portions either of the entodermal lining of the pouch or of the ectodermal lining of the cleft; the latter often gives rise to an epidermoid malignant growth.

Progress in Pediatrics

ADAMANTINOMA OF THE CRANIOPHARYNGEAL DUCT

OCCURRENCE IN A CHILD MANIFESTING MARKED CACHEXIA AND DYSPITUITARISM OF THE LORAIN TYPE

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The early diagnosis of intracranial tumors in children is not easy, and it is often impossible. Frequently, obscure symptoms are the only clinical evidences of a pathologic intracranial process, and they are likely to be considered to result from some other cause more commonly encountered in general practice. Even in the presence of unquestionable evidence of tumor of the brain there is at times delay in making the correct diagnosis. Crucial data are either misinterpreted or are not obtained.

The case to be presented in this paper illustrates particularly that tumors involving the floor of the third ventricle may produce disturbances in growth and nutrition. Cachexia, which was the most outstanding symptom in the case, is rare as compared with adiposity, which is the usual manifestation of endocrine dysfunction associated with suprasellar tumors. Few cases in which such a tumor occurred in a young child and cachexia was manifest have been reported.

REPORT OF CASE

C. C. L., a white girl aged 6½ years, was admitted to the Indianapolis City Hospital on June 28, 1938. She complained of headache, vomiting, somnolence and rapid loss of weight and manifested, at admission, features of stunted growth and marked cachexia. Late in her illness signs of increased intracranial pressure and neurologic observations suggested a lesion in the posterior cranial fossa. A suboccipital exploration and decompression done Jan. 10, 1939 did not reveal a subtentorial lesion, but signs were present of marked pressure on the brain stem from above the tentorium. The child died during the operation. Necropsy revealed a tumor of the hypophysial stalk, lying retrochiasmally and invaginating into the third ventricle. Pressure changes on the surrounding structures, including the sella turcica and the hypophysis, were present. Microscopic examination showed that the tumor was a typical adamantinoma of the craniopharyngeal duct and that organic changes in the pituitary body were present.

From the Pediatric Department of the Indianapolis City Hospital.

History.—The patient was born Nov. 24, 1931, of Jugoslavian parentage, and was the fifth of 7 children. She was spontaneously delivered at full term; she was small at birth but apparently normal in all respects immediately after delivery. There were no childhood diseases other than measles, which was followed by pneumonia, when the patient was 18 months old. She was always retarded in growth, being smaller than the other children of her age. Her appetite was poor throughout her life. The family history is essentially noncontributory except from the economic point of view. The father earned low wages and the family had little to live on. There was not much variety in the types of food eaten.

During the spring of 1938, the patient began to have nocturia and complained of thirst. There was a rapid loss of weight, and at the time of admission to the hospital emaciation was marked, the abdomen having become scaphoid and the appearance of the whole body changed. Two days previous to admission, the child complained of intense occipital headache, which was followed by vomiting, projectile in type. She had never had headache or vomited before, and no visual disturbance had been complained of or noticed. The child was admitted to the contagious disease ward of the hospital because of the possibility of tuberculous meningitis.

Physical Examination.—The patient was too weak to walk, being barely able to stand alone. She perspired freely and complained of being cold. She preferred to lie on her side, with her head drawn backward and her legs flexed on her abdomen. The headache must have been severe for she moaned continuously. Marked photophobia was noticed the day of admission, and the vomiting persisted. Some difficulty in breathing was also noted. The neck was held rigid. No nystagmus was noticed. Her eyes reacted to light and in accommodation. The fundi were not seen because the patient could not cooperate. The tonsils were hypertrophied and the pharynx injected. The teeth were in poor condition, most of them showing decay at the gingival margins. The pulmonary fields were clear. The heart sounds were regular and without murmurs; there was no cardiac enlargement. The abdomen was free of palpable masses and tenderness. The external genitalia were inflamed, and a vaginal discharge was present. There was no abnormality of the extremities other than marked emaciation. The tendon reflexes were hyperactive.

The most impressive observations were apparent arrest of general development and marked cachexia. She was a delicate undersized child with the body proportions of an adult. The long bones, although shorter than normal for her age, were all in proportion to the rest of the body, and roentgen examination later showed that the centers of ossification were close to normal. The patient's head seemed large in comparison with her emaciated body. Because of the small amount of subcutaneous fat the whole body had lost its childish contour, and the cordlike muscles and skeletal features were prominent. The intercostal spaces were sunken inward, so that a rachitic rosary on each side was evident. The extremities were markedly emaciated.

Laboratory Examination.—Complete examinations of the spinal fluid gave essentially normal results at the time of admission, as did urinalyses, blood counts and serologic tests of the blood. Examination of the vaginal discharge was negative for pathologic organisms. The intake and output of fluids were recorded each day during the entire stay in the hospital. The average figures for twenty-four hours were 1,400 and 750 cc., respectively. The specific gravity of the urine was

normal. The pulse and respiratory rates were not unusual. Practically all of the temperature readings were subnormal, some being as low as 97 F. Only a few were above 98.6 F., and the highest was 99.8 F.

Course.—The child was placed on a diet high in calories and vitamins and was given vitamin B complex, cod liver oil and as much orange juice as she would take. The symptoms present at admission subsided after she had been in the hospital for a few days; her appetite improved, and apparently there was some gain in weight. She was considered to have nutritional deficiencies, and after she had shown some improvement she was released (July 25), arrangements having been made to place her in a boarding home on a farm, where she could have the advantages of proper food and a healthful environment. There she was fed plenty of fruit juices, nursery milk, steak, eggs and various leafy vegetables. Although her vitality increased, she gained but 1 pound (454 Gm.) in the five weeks she was in the foster home.

Second Admission.—On August 31 she was brought to the hospital again for a preliminary examination preparatory to the extraction of some teeth which were in poor condition. Because of her frailness and evident malnutrition, hospitalization for several days before dental extraction was recommended. Before the day appointed for admission, however, she had a recurrence of the previous symptoms of headache, lassitude, nausea and vomiting, and her weakness increased. She was readmitted on September 3. As on the first admission to the hospital, these symptoms subsided after she had been in the ward for a few days. Her management was much the same as before.

Her small size may have been partially responsible for the impression that her intelligence was above the average for her age, but she was far from being dull mentally. Her memory for events and for persons' names was excellent. She always showed interest in the things about her and in the events which took place in the ward. For the most part she was cooperative.

Diagnostic impressions ran the gamut from malnutrition through chronic infection, endocrine disturbances, celiac disease, disturbance of the cystine metabolism, Simmonds' disease and anorexia nervosa to some type of diencephalic syndrome, which proved to be the correct diagnosis.

The patient was weighed twice weekly. The weight at admission (September 3) was 21½ pounds (9.75 Kg.), and it showed little change. On the day before operation (Jan. 10, 1939), one hundred and twenty-nine days after the second admission, she weighed 21¼ pounds (9.63 Kg.). School records showed that on Oct. 22, 1937 the child had been 38¾ inches (97.4 cm.) tall and had weighed 25¾ pounds (11.68 Kg.). At intervals she complained of hunger, but even then she did not eat heartily. Several methods were employed to encourage her to take all the food offered. From a record of the actual number of grams of each food eaten it was estimated that the child received an average of at least 40 to 60 calories per pound (454 Gm.) per day throughout her stay in the hospital. Several unsuccessful attempts were made to obtain a satisfactory determination of her basal metabolic rate.

The intake and output of fluids were recorded for three weeks and were found to be essentially the same as on the previous admission, except that the records of output became less accurate as the child became progressively more careless about voiding in bed. Later, urination became involuntary. The urinalyses, which were performed at intervals, gave essentially normal results.

Roentgenographic Examination.—A flat roentgenogram of the chest (taken September 13) revealed a few small areas of density in the region of the inferior bronchus on the right side and a slight increase in all of the pulmonary markings, but no pathologic change suggesting tuberculosis was seen. On September 24 roentgenograms were taken of the skull to determine whether changes had taken place in the sella turcica. Although there were signs of rarefaction of the flat bones of the skull, the sella turcica showed no abnormality. Roentgenograms of the spine, the ribs and the upper extremities were likewise negative for bony changes.

Fig. 1.—Patient late in the course of the illness. Cachexia was marked.

Laboratory Examinations During Second Admission.—The blood counts varied from time to time. The hemoglobin content (Dare) averaged 70 to 83 per cent; the number of erythrocytes ranged from 3,620,000 to 4,590,000 and the number of leukocytes from 5,900 to 12,050. Differential counts showed 21 to 50 per cent lymphocytes, 42 to 75 per cent monocytes, 0 to 9 per cent eosinophils and 0 to 2 per cent basophils. Results of chemical examinations on the blood were repeatedly normal. The sedimentation rate on September 7 was 9.5 mm. after sixty minutes. Agglutination tests for the typhoid bacillus and for types A and B of the paratyphoid bacillus gave negative results. Examinations of fecal specimens were negative for fat and for animal parasites or ova. A dextrose tolerance

test was done on October 4; 15.5 Gm. of dextrose was given in orange juice. The fasting blood sugar was 68 mg. per hundred cubic centimeters; specimens taken half an hour and one, two and three hours after the ingestion of the dextrose showed blood sugar levels of 125, 177, 186 and 66 mg., respectively. The blood calcium on October 10 was 9.6 mg. per hundred cubic centimeters. On December 12 the total protein content of the blood was 7.8 mg. per hundred cubic centimeters, the serum phosphate was 3.4 mg., the serum calcium was 9.7 mg. and urinalysis did not reveal cystine. On December 16 the blood urea nitrogen was 12.2 mg. per hundred cubic centimeters; the standard urea clearance was 16 cc. of blood cleared per minute; the percentage of the average normal standard clearance was 29.6; with a correction for body surface area, the percentage of the average normal standard clearance was 86. The reactions to the Mantoux test were repeatedly negative.

Course During Second Admission.—Although the patient had headache and vomiting, these symptoms were transient, occurring in bouts at irregular intervals. On both admissions these symptoms subsided within a few days. Recurrences of the headache were recorded in the bedside notes, and mention is made that the child complained of this symptom only on August 20 and 21; October 4, 13, 18, 21, 30 and 31; November 16 and 17; December 28, and January 6. Vomiting occasionally accompanied the headache. At no time was any difficulty in vision noticed when headache was present. During the intervals between the paroxysms of headache the patient had no complaints except weakness. She was allowed to be up in a wheel chair or to walk, but she preferred to stay in bed. She became exhausted easily and was always tired at the end of the day. She had a tendency to sleep much of the time.

The poor teeth, for the extraction of which the child was readmitted, were considered a result, and not a cause, of the general condition. Two molars were extracted, but the front teeth were allowed to remain in spite of their poor condition. The specific medicaments given consisted of vitamin preparations, liver and thyroid extracts, and hematonic substances. Administration of a preparation containing the growth-producing principle of the anterior lobe was suggested but not carried out.

Visual disturbances were noticed for the first time on January 7, when it was seen that the patient had a vacant stare. Simple tests showed that the child was totally blind, even for light perception. The pupils did not react to light. Ophthalmoscopic examination revealed bilateral papilledema, 4 D.

Neurologic Examination.—Spinal puncture was performed to determine the fluid tension. The opening pressure was 370 mm. of water. A bilateral Queckenstedt sign was present, the pressure of the spinal fluid rising 45 and 35 mm., respectively, when the right and the left side were tested. The patient was cooperative during the first part of the examination, but she began to struggle and cry after 10 cc. of fluid had been cautiously drained off, so a closing pressure was not obtained. The patient experienced no distress after the removal of the fluid. The laboratory report on the specimen of fluid indicated that it was normal except for the globulin content (2 plus).

On neurologic examination Dr. E. Vernon Hahn, consultant in neurology to the hospital, verified the results of ophthalmic examination and observed that the pupils were in middilatation and almost fixed to light but varied in accommodation. There was no nystagmus, ptosis or strabismus. Rotations were normal.

Macewen's "cracked pot" sign was present. The frontal and occipital bosses were enlarged. The knee jerks were absent. The abdominal reflexes were present. The toe reversal signs of Babinski, Oppenheim and Gordon were positive bilaterally, less pronounced on the left side. Bilateral ankle clonus was present. The patient walked and stood with a wide base. The Romberg sign was positive. The coordination of the upper extremities, as tested by the finger to nose and finger to finger exercises, was fairly good. The signs and symptoms suggested the presence of a tumor of the posterior cranial fossa.

Ophthalmologic Consultation.—The patient was seen the same evening by Dr. Robert J. Masters, consultant in ophthalmology to the hospital, and he suggested that any surgical procedures directed toward a reduction of the papilledema might improve the vision and should be carried out before prolonged pressure caused permanent damage. Consequently, an operation was scheduled for the following day, January 10.

Second Roentgenographic Examination of the Head.—The child was cheerful during the morning, professing that she could see better. Simple tests proved that this was not true. Roentgenograms of the head showed marked increase in the intracranial pressure. The coronal suture was separated, the width being about 0.5 mm. No calcification or changes in the sella turcica were observed.

Operation.—On opening the posterior cranial fossa it was observed that the bone was extremely thin. The dura was under terrific pressure. The cerebellum bulged out of the incision made in the dura. The left cerebellar hemisphere was much larger than the right. The cerebellar tonsils were herniated into the foramen magnum, which necessitated resection of the arch of the atlas to guard against postoperative pressure on the medulla. No tumor mass was observed in the abnormal-looking left cerebellar hemisphere on inspection, exploration with a needle or incision by the electric cutting current. It became apparent that the lesion must be at, or above, the aperture of the tentorium cerebelli and ventrally placed, so that it occluded the aqueduct of Sylvius by upward pressure on the brain stem. The surgical wound was closed, but the child died before the operation was completed.

Necropsy.—The external appearance of the body was unchanged except for the shaved scalp and the semicircular surgical incision over the occiput. There were no demonstrable pathologic changes in any of the body tissues or organs outside of the cranium, except that a right hilar lymph node showed tuberculous changes. Subcutaneous fat was present only in a minimal amount, and there was little extraperitoneal and omental fat. The body did not appear microsplanchnic.

The calvarium was removed above the area of decompression. The bones of the cranial vault were thin and fairly dense, with little diploe between the inner and the outer table. The brain, with the tumor mass, was removed *in toto* (weight, 998.8 Gm.). The left hemisphere was larger than the right, and the whole brain was swollen and pale. The convolutions were flattened, and the blood vessels were not prominent.

The tumor mass was yellowish white and lobulated. It extended downward from the interpeduncular region and forward to incorporate the tuber cinereum and to abut retrochiasmally (fig. 2). After the brain had hardened in solution of formaldehyde U. S. P., the hemispheres were divided sagittally, a procedure which also divided the tumor mass. The tumor invaginated into, and almost filled, the

third ventricle. The lateral ventricles were dilated. The cut surface of the tumor was spongelike; it contained small cysts in some parts but consisted mostly of solid tissue. No large calcified nodules or necrotic areas were found on gross examination, and no exceedingly large cysts were demonstrated. The mass did not have a particularly well formed capsule.

Pressure from the tumor, because of its retrochiasmal position, seemed to have flattened and compressed the optic chiasm forward, but the optic nerves appeared to be normal at their exit over the clinoid processes. The abducens nerves appeared normal; they swung deep posteriorly to the tumor and anteriorly to the pons. The pons itself appeared much compressed in the anteroposterior diameter. No distortion of the olfactory tracts was noted. The blood vessels at the base of the brain were small. There was evidence that the tumor bulged posteriorly,

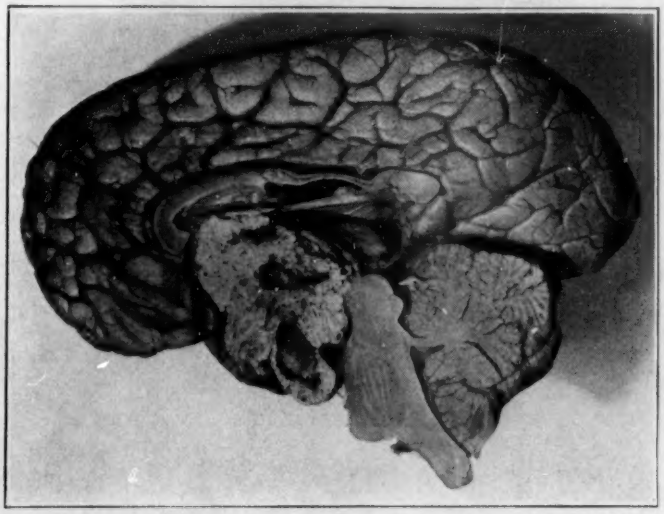

Fig. 2.—Midsagittal section of the brain. The tumor mass invaginates into and almost fills the third ventricle. Note the spongelike consistency of the tumor and the moderate-sized cyst in its lower portion.

pushing the cerebral peduncles and the brain stem backward through the aperture of the tentorium cerebelli.

The sella turcica was 1.8 cm. in the transverse diameter, 2 cm. in the anteroposterior diameter and 1 cm. deep. The cavity was circular. The right posterior clinoid process was eroded away and the left projected only 0.1 cm., as a rounded upper border of the posterior wall of the sella turcica (fig. 3). The aperture of the tentorium of the sella turcica measured 0.3 cm. The stalk of tissue which filled this opening appeared to have the same composition as the tumor mass and seemed to be continuous with a compressed mass of tissue, 1.1 cm. in diameter, visible through the tentorium.

The base of the skull surrounding the hypophysial region was removed in one piece (fig. 3) and the block of tissue placed in a fixative solution. Later, the hypophysis was dissected free and microscopic sections made.

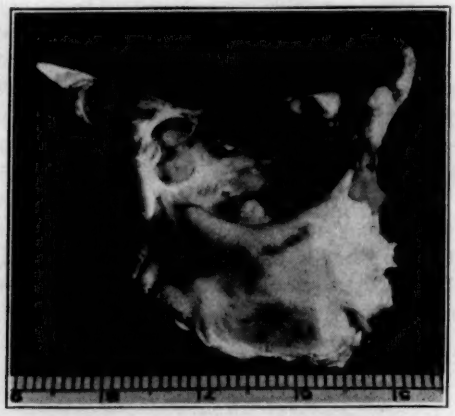

Fig. 3.—The sella turcica. The optic nerves can be seen superiorly at their exit over the anterior clinoid processes. Anterior and inferior to the posterior clinoid processes is a stalk of tumor tissue filling the aperture of the tentorium of the sella turcica. The right posterior clinoid process has been eroded away by the pressure of the suprasellar tumor.

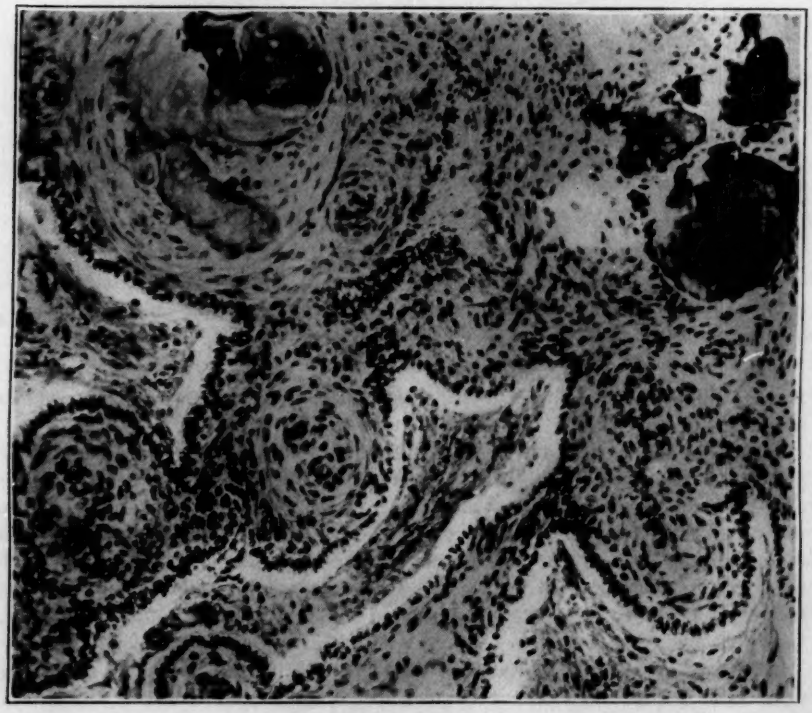

Fig. 4.—Microscopic section of a solid portion of the tumor mass. Note the characteristic arrangement of the epithelial cells, the evidences of degeneration and the calcification.

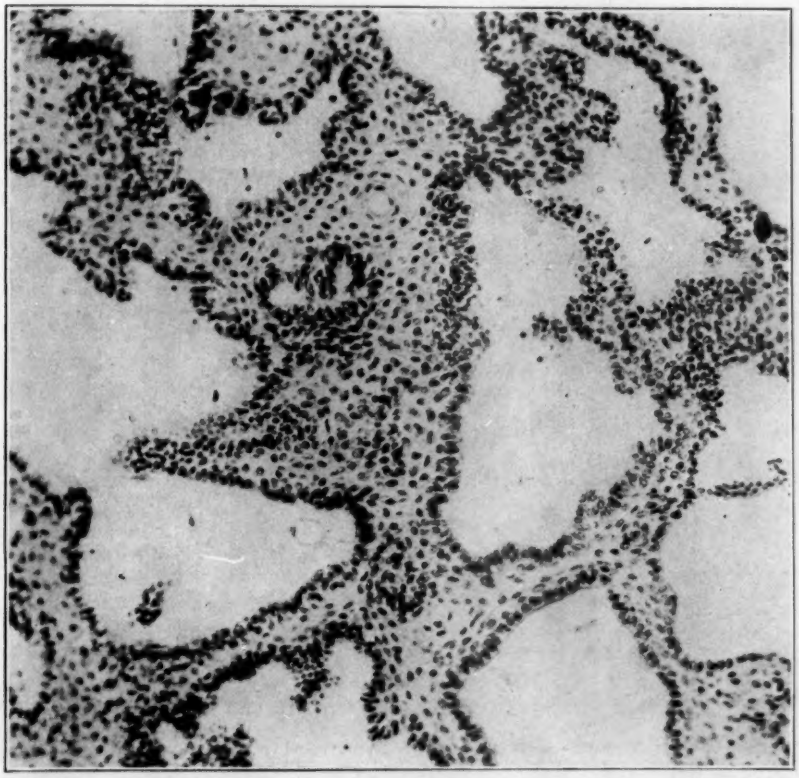

Fig. 5.—Typical microscopic section of the cystic portion of the tumor mass.

Fig. 6.—The tumor mass. Note the tendency to cyst formation. Low magnification.

Fig. 7.—Microscopic section showing the typical cellular arrangement of the epithelial tree.

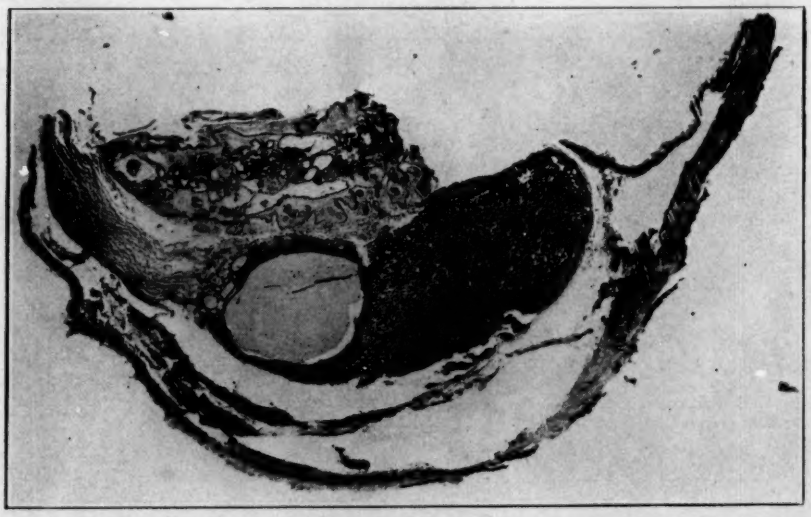

Fig. 8.—Sagittal section through the pituitary body. The tumor tissue has invaded the posterior lobe and compressed the anterior lobe.

Microscopic Examination: Dr. H. C. Thornton, chief pathologist of the hospital, pointed out that the gross and microscopic studies of the tumor mass confirmed the diagnosis of adamantinoma of the craniopharyngeal duct. The microscopic appearance was typical of such tumors. The epithelial cells constituting the basic structure were arranged in columns which had a marked arborescent tendency; they spread out and formed many branching lobules which intertwined and anastomosed. Between these columns there was more or less abundant stroma. Figures 4 and 5 are typical sections of this epithelial tree. The basilar layer was composed of columnar cells, sharply demarcated outwardly from the stroma. The columnar cells had a pale cytoplasm and oval nuclei, with a moderate amount of chromatin. The cells inside the basal layer of columnar cells resembled squamous epithelium. This resemblance was strengthened in places by the presence of intercellular bridges and atypical pearly bodies, many of which had accumulated lime salts and were definitely undergoing calcification. Centrally placed in some of the columns was a loose syncytial arrangement of stellate cells with vesicular oval nuclei and cytoplasmic bridges, somewhat similar to primitive mesenchyme. However, in most of the columns the cells were rather compactly arranged. The epithelial columns ranged in size from thin cordlike structures to plump epithelial growths.

The stroma varied in abundance and appearance. There were distinctly fibrillar portions in some places; in others it had a myxomatous appearance and showed cystic degeneration. The number of cells within the stroma was not great. Most of them were fibroblastic and mononuclear, with "foamy" cytoplasm.

Thus, as is common in tumors of the hypophysial stalk, the tissue showed evidence of degeneration, cyst formation and calcification. It is known that calcification is present in almost all such tumors and usually is so abundant that it may appear in every microscopic field. The granules range in size, however, from small particles to conglomerations, or large irregular calcified masses, which are easily revealed by roentgen examination of the sellar region. Bone is even said to occur in such tumors.

Multiple small cysts lay among the epithelial columns. Apparently the cysts in this case were formed as a result of degenerative changes in the stroma. Epithelial masses are seen intact in figures 5 and 7. The stroma was loose, almost acellular and cystic.

Microscopic examination of the pituitary body showed invasion of the posterior lobe by tumor tissue. The anterior lobe was compressed (fig. 8).

No changes were observed in other parts of the nervous system.

INCIDENCE

Since tumors of the hypophysial stalk are congenital, one would expect to find the majority of these lesions in children and adolescents. They are the most frequent tumor of the supratentorial cavity in children (Bailey[1]), but it is well known that they are not the most common tumor of the brain. Most of the tumors in childhood are of the cerebellum. Also, it is to be remembered that although these tumor masses

1. Bailey, P.: The Tumors of the Nervous System, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1940, vol. 4, chap. 21.

are congenital they are not always diagnosed in early life. They rarely cause symptoms in infancy. Of 1,108 cases of verified intracranial tumor studied by Cushing,[2] the diagnosis was made in only 154 in preadolescence, and of these 154, the tumor was congenital in only 21. Different classifications of the tumors of the hypophysial stalk have been made (Duffy,[3] Frazier and Alpers [4]). The adamantinomas are one of the types of heterogenous hypophysial tumors arising from cells not actually part of the glandular tissue. They comprise possibly half of the tumors originating in the hypophysial duct. As will be seen, they arise from the same oral epithelium of the embryo as do the dental lamina and the embryonic enamel organ. The similarity of the tumor to these structures is striking in some instances, hence the name adamantinoma of the craniopharyngeal duct. The term craniopharyngioma is also used for this tumor. Apparently only a few of the adamantinomas cause symptoms of stunted growth and manifest cachexia. Frazier [5] found only 1 case of so-called pituitary cachexia in a series of 216 cases of primary pituitary lesions and tumors of the pharyngeal duct. Beckmann and Kubie [6] found that in 2 of 12 cases of adamantinoma there were emaciation and weakness. The youngest patient with adamantinoma of the craniopharyngeal duct who showed emaciation is said to be that of Olivecrona (Frazier and Alpers [4]). This patient was 5 years old.

EMBRYONIC DEVELOPMENT OF THE HYPOPHYSIS

Tilney [7] has shown that the hypophysis of all vertebrates, from the lowest to man, is constant in its fundamental constituents and mode of development. He and others (Duffy,[8] Erdheim,[8] Critchley and Iron-

2. Cushing, H.: The Intracranial Tumors of Preadolescence, Am. J. Dis. Child. **33**:551-584 (April) 1927.

3. Duffy, W. C.: Hypophyseal Duct Tumors: A Report of Three Cases and a Fourth Case of Cyst of Rathke's Pouch, Ann. Surg. **72**:537-555 (Nov.); 725-757 (Dec.) 1920.

4. Frazier, C. H., and Alpers, B. J.: Adamantinoma of the Craniopharyngeal Duct, Arch. Neurol. & Psychiat. **26**:905-965 (Nov.) 1931.

5. Frazier, C. H.: (*a*) A Series of Pituitary Pictures: Commentaries on the Pathologic, Clinical and Therapeutic Aspects, Arch. Neurol. & Psychiat. **23**:656-695 (April) 1930; (*b*) Pituitary Cachexia, ibid. **21**:1-18 (Jan.) 1929.

6. Beckmann, J. W., and Kubie, L. S.: A Clinical Study of Twenty-One Cases of Tumor of the Hypophyseal Stalk, Brain **52**:127-169 (July) 1929.

7. Tilney, F.: The Development and Constituents of the Human Hypophysis. Bull. Neurol. Inst. New York **5**:387-436 (Aug.) 1936.

8. Erdheim, J.: Ueber Hypophysenganggeschwülste und Hirncholesteatome, Sitzungsb. d. k. Akad. d. Wissensch. Math-naturw. Cl. **113**:537-726, 1904

side [9]) have given admirable reviews on the embryonic development of this structure and have pointed out how the so-called tumors of the pituitary stalk may originate from embryonic remnants.

The hypophysis cerebri arises from two specialized sources of ectoderm, the somatic ectoderm in and about the junction of the pharyngeal membrane with the roof of the primitive stomodeum and the neural ectoderm in the floor of the third ventricle. The neural component develops into the pars posterior of the hypophysis. Its stalk, unlike that of the stomodeal component, does not disappear but persists as the infundibulum of the tuber cinereum, which is a thin layer of gray matter alone separating the pituitary fossa from the cavity of the third ventricle.

From the primitive oral cavity there forms an invagination, known as Rathke's pouch, which passes upward in front of the notochord and between the trabeculae cranii to the base of the brain. The neck, or stalk, of this pouch becomes constricted as the sphenoid bone develops and by this means is as a rule entirely destroyed, leaving the pouch closed and entirely shut off from the oral cavity. The closed pouch, or sac, flattens out against the infundibular process and grows rapidly to enclose the neural component. The ventral wall of the pouch thickens greatly and becomes converted into a solid glandular structure forming the pars anterior of the hypophysis. The dorsal wall is closely applied to the infundibular process and becomes the pars intermedia, which may be small or even absent in man. Lateral extensions of the pouch grow up to enclose the infundibular stalk and constitute the pars tuberalis.

Carmichael [10] studied 55 normal hypophyses removed at necropsy and found masses of cells resembling squamous epithelium in histologic appearance in 18. Susman [11] found that 71 of 230 adult human hypophyses had such epithelial cell rests. It is reasonable to attribute the origin of such groups of cells to remnants of the former hypophysial stalk connecting the primitive Rathke's pouch with the oral cavity. The site of insertion of the stalk into the pouch appears to have been carried upward and forward with the developing pars tuberalis and thus to have come to lie in the region of the lower third of the infundibulum, or even at its union with the tuber cinereum at the base of the brain in or near the midline. It is in this situation that most of the masses of cells resembling squamous epithelium are found, and it is here that some of the tumors of the hypophysial stalk apparently arise.

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9. Critchley, M., and Ironside, R. N.: The Pituitary Adamantinomata, Brain **49**:437-481 (Dec.) 1926.

10. Carmichael, H. T.: Squamous Epithelial Rests in the Hypophysis Cerebri, Arch. Neurol. & Psychiat. **26**:966-975 (Nov.) 1931.

11. Susman, W.: Embryonic Epithelial Rests in the Pituitary, Brit. J. Surg. **19**:571-576 (April) 1932.

PATHOLOGY AND SYMPTOMATOLOGY

Since the location, the direction of growth and the eventual size of these tumor masses are all variable factors, the symptoms resulting from organic changes and disturbance in function of the surrounding tissues are likewise variable. Tumors immediately affecting the third ventricle may cause characteristic symptoms by pressure on its walls and their contained nuclei and tracts or may cause other symptoms by interference with the circulation of the cerebrospinal fluid through hindrance of the venous return from the choroid plexus or by obstruction of the outlets of the ventricle. Symptoms of the latter type are usually spoken of as general pressure symptoms caused by the resulting internal hydrocephalus. Of such symptoms, headache, vomiting, choking of the optic disks with secondary optic atrophy, somnolence and enlargement of the head are by far the most frequent in young children (Bailey [1]). Since they are almost never absent, they will be considered first.

Usually, the first symptom of the tumor in childhood is headache. It ordinarily manifests itself in bouts and may be accompanied by vomiting and visual disturbances. In the clinical report of Beckmann and Kubie [6] on 21 cases of tumors of the hypophysial stalk it was mentioned that 7 of the 9 youngest patients had bouts of diffuse headache. Of these 7 patients 4 showed papilledema as evidence of increased intracranial pressure, but none of the other patients had such opthalmoscopic changes. It is well known that intracranial lesions in children are likely to cause secondary hydrocephalus, and this is the reason that such symptoms as headache and vomiting are much more common in young patients than in adults. The headache in children and adolescents is diffuse and generalized. In older patients there is a tendency for the pain to localize, but because the headache is variable in duration, intensity and location, even in the same patient, this symptom offers little help in differential diagnosis. It usually is aggravated by anything which tends to raise intracranial pressure, such as stooping, coughing, straining or crying. Vomiting or enlargement of the head may precede the onset of headache. The vomiting is typically cerebral, being practically always forcible; it may or may not be preceded by nausea; it appears mainly in the early morning but may occur at any time and bears no relation to the ingestion of food. The child may be refed immediately after vomiting and retain the food perfectly.

Primary optic atrophy from direct pressure may be present, but papilledema secondary to intracranial hypertension is more common in children; it occurs in 80 per cent of all cases of cerebral tumor in children (Critchley [12]). It is apt to appear abruptly, as an acute and

12. Critchley, M.: Brain Tumors in Children: Their General Symptomatology, Brit. J. Child. Dis. **22**:251-264 (Oct.-Dec.) 1925.

high grade swelling of 4 to 5 D., occurring most often simultaneously in both eyes. When the visual symptoms come on asynchronously, the time interval between their appearance in the two eyes is never long if the cause is a tumor of the hypophysial stalk. High intracranial tension before much destruction of the optic nerve fibers has occurred may produce uncomplicated choking of the disks with perfect vision.

Cushing and Walker [13] reported 101 cases of lesions of hypophysial or parahypophysial origin and showed that in 81 the lesion produced chiasmal involvement leading to deformations of the fields of vision. The defect produced varies with the location of the tumor and with the amount of pressure on the different portions of the optic chiasm and nerves. Most authors agree that bitemporal hemianopia is the most common defect of the visual field. This is usually not exactly symmetric on the two sides. Cushing demonstrated that the defect begins in the upper temporal quadrant, progresses to the inferior temporal quadrant and later involves the nasal fields. In all stages the loss of perception of color is usually in advance of that of form, and the condition in one eye is usually in advance of that in the other. The failure to observe visual symptoms until blindness is total prevents the recognition of bitemporal hemianopia, which probably at one time is present in every case. Although no visual disturbance is complained of, the presence of this condition may often be inferred from the fact that subjects with hemianopia usually turn the head far more in order to look to the side than do people with normal vision and that they often bump into objects on either side of them. Determinations of the visual fields in children are not always reliable. Young patients sometimes do not cooperate, and the papilledema, too, often makes examination impossible. The presence or absence of choking of the disks, an important ocular symptom in children, however, can and should be determined.

Bailey [1] and others have emphasized that since the sutures of the calvarium do not become firmly closed until near puberty, any increase in the intracranial tension may be immediately reduced by separation of the sutures. This spontaneous decompression may be produced by only a slight increase in intracranial tension in young children, and thus the cardinal symptoms of headache, vomiting and failing vision are often absent, inconspicuous or only transitorily present. A child may often appear to be so well in spite of his bouts of vomiting and weakness that causes other than tumor of the brain are suspected. Children are not so prone as adults to complain of a slight obscuration of vision, and the discovery of an advanced grade of choked disk may come as a total

13. Cushing, H., and Walker, C. B.: Distortions of the Visual Field in Cases of Brain Tumor: Chiasmal Lesions with Special Reference to Bi-Temporal Hemianopia, Brain **37**:341-400, 1915.

surprise. Vomiting is apt to be a dominant feature in such cases at the onset and indeed may be regarded as a symptom of localizing value.

It will be recalled that somnolence, polydipsia and nocturia were among the early symptoms noticed in the case reported. A hypothalamic syndrome consisting of hypersomnia, polyuria, adiposity, genital dystrophy, and perhaps also glycosuria and circulatory disturbances, may be produced early by tumors arising in the infundibulum of the hypothalamus (Camus and Roussy,[14] Bailey and Bremer,[15] Smith[16] and Futcher[17]). Although primary hypophysial tumors not projecting into the third ventricle may cause apathy, lethargy and lassitude from lowering of the metabolism (Peet[18]), there is evidence which makes it doubtful whether the hypophysis plays an essential role in the production of hypersomnia, adiposity and genital dystrophy unless a tumor grows large enough to produce secondary involvement of the basal region of the brain. Erdheim[8] showed that the tumor which usually causes the syndrome of Fröhlich was congenital in origin and suprasellar in situation; and since it is prone to deform the interbrain, he was led to attribute the syndrome largely to a diencephalic, rather than a glandular, source. Cushing[19] and Ranson, Fisher and Ingram[20] expressed the belief that the hypothalamus regulates the secretory activity of the posterior lobe of the hypophysis through a tract of nerve fibers, the supraopticohypophysial system, descending from the hypothalamus into the neural division of the hypophysis. An antidiuretic hormone has been shown to be present in the posterior lobe (Fisher[21]). It is thought that this antidiuretic hormone acts on the kidneys and prevents them from secreting an excessive amount of urine. Diminution in the amount

14. Camus, J., and Roussy, G.: Experimental Researches on the Pituitary Body: Diabetes Insipidus, Glycosuria, and Those Dystrophies Considered as Hypophyseal in Origin, Endocrinology **4**:507-522 (Oct.-Dec.) 1920.

15. Bailey, P., and Bremer, F.: Experimental Diabetes Insipidus, Arch. Int. Med. **28**:773-803 (Dec.) 1921.

16. Smith, P. E.: The Disabilities Caused by Hypophysectomy and Their Repair: The Tuberal (Hypothalamic) Syndrome in the Rat, J. A. M. A. **88**:158-161 (Jan. 15) 1927.

17. Futcher, T. B.: The Etiology and Treatment of Diabetes Insipidus, Ann. Int. Med. **5**:566-573 (Nov.) 1931.

18. Peet, M. M.: Pituitary Adamantinomas, Arch. Surg. **15**:829-854 (Dec.) 1927.

19. Cushing, H.: The Pituitary Gland as Now Known: Cameron Prize Lecture, New York, Oxford University Press, 1925, lecture 2.

20. Ranson, S. W.; Fisher, C., and Ingram, W. R.: The Hypothalamico-Hypophyseal Mechanism in Diabetes Insipidus, A. Research Nerv. & Ment. Dis., Proc. (1936) **17**:410-432, 1938.

21. Fisher, C.: The Site of Formation of the Posterior Lobe Hormones, Endocrinology **21**:19-24 (Jan.) 1937.

of this hormone through injury to the supraopticohypophysial system or the hypothalamus brings about primary polyuria, which is followed by compensatory and secondary polydipsia. The results of the experimental studies of the authors mentioned support this conception. Typical dyspituitary syndromes have been produced by injury to the tuber cinereum above the pituitary gland, the latter being left intact. Several clinical cases have been reported in which diabetes insipidus, glycosuria, adiposity and Fröhlich's dystrophia adiposogenitalis were observed in association with lesions of the hypothalamus when, judged by the results of histologic examination, the pituitary body was normal (Worster-Drought, Dickson and Archer [22]). If physiologists are correct in believing that the hypothalamus is a great head ganglion of the vegetative nervous system (Cannon [23]) and if the deduction can be made that it also governs the pituitary gland, with its multiple endocrine functions, it is evident that a disturbance in the normal functioning of this part of the brain can have various and far reaching effects. The intake and output of fluids in the case reported were not in keeping with true diabetes insipidus. The urinary specific gravity was constantly moderately high. Ranson, Fisher and Ingram [20] pointed out that diabetes insipidus occurs in the absence of the neural division of the hypophysis only if tissue of the pars anterior is present. Further growth of the tumor might have compressed the anterior lobe enough to have stopped the urinary mechanism which gives rise to the symptoms typical of diabetes insipidus.

The signs of pituitary dysfunction in the order of frequency in 14 cases of adamantinoma reported by Frazier and Alpers [4] were: dwarfism, 7; somnolence, 6; adiposity, 5; regressive sex characteristics, 4; feminizations, 4; polyuria, 3; amenorrhea, 1, and emaciation, 1. This distribution is in agreement with that reported by other authors in that arrest in normal growth was the commonest sign of endocrine disturbance.

At least three principles elaborated by endocrine glands are known to play important roles in growth and development. Two of these, namely, the growth-stimulating hormone and the gonadotropic hormone, are elaborated by the anterior lobe of the hypophysis. The secretion of the thyroid gland is the third. Little is definitely known yet concerning the relation of the other endocrine principles to growth.

22. Worster-Drought, C.; Dickson, W. E. C., and Archer, B. W. C.: Dyspituitarism of the Lorain Type, Associated with a Pituitary Cyst Arising from Rathke's Cleft and Secondary Lesions in the Hypothalamic Regions and Ventricles, Brain **50**:704-718 (Oct.) 1927.

23. Cannon, W. B.: Neural Organization for Emotional Expression, in Symposium on Feeling and Emotions, Clark University Publications, Worcester, Mass., May 1927.

The gonad-stimulating hormone of the anterior lobe of the pituitary is a general sex hormone which acts on both the male and the female. In the male the effects of this principle are manifested by the descent of the testes and the general growth of the interstitial cells of Leydig and by the stimulation of the germinal epithelium with the onset of gametokinetic activity. In the female this hormone stimulates the maturational progress of the primordial follicles toward the graafian state and acts by the formation of lutein cells in the follicles when they have attained a certain stage in their maturation. The normal menstrual cycle depends on the response of properly developed and matured gonads to the cyclic stimulation of a normally functioning hypophysis. If there is dysfunction of the hypophysis caused by pressure from lesions, such as tumors, amenorrhea and impotence are apt to occur. Such symptoms are constant in older patients with tumors of the hypophysial stalk. In the child and the adolescent the absence or insufficiency of the secretion of the gonadotropic factor will prevent the normal development of ovarian and testicular tissue. Cryptorchidism in the male and primary amenorrhea in the female, with resultant delayed puberty and failure of secondary sex characteristics to appear, are believed to be due to inadequate production of this hormone.

The growth-stimulating hormone of the pituitary is believed to be the controlling factor in the growth of every body structure, including the individual cell. The cytologic source is the eosinophilic cell, and the principle is apparently gland specific, since it has not been derived from any other source. Lee [24] suggested that the essential and primary characteristics of true growth may be regarded as the formation and deposition of body protein. The unique action of the anterior lobe of the pituitary gland in stimulating body growth and the complete failure of true growth in its absence suggest that the growth-stimulating hormone is an essential part of the mechanism controlling the synthesis, deposition and utilization of protein in the tissues. Other writers, such as Freud, Levie and Kroon,[25] have expressed the belief that the area characteristically affected by the action of the growth-stimulating hormone is the proliferating cartilage of the developing osseous system. It is generally agreed that the administration of an extract containing the growth-stimulating substance is of no value after the epiphyses have closed. Evans and Long [26] first recognized and demonstrated the sub-

24. Lee, M. O.: Relation of Anterior Pituitary Growth Hormone to Protein Metabolism, A. Research Nerv. & Ment. Dis., Proc. (1936) **17**:193-221, 1938.

25. Freud, J.; Levie, L. H., and Kroon, D. B.: Observations on Growth (Chondrotrophic) Hormone and Localization of Its Point of Attack, J. Endocrinol. **1**:56-64 (June) 1939.

26. Evans, H. M., and Long, J. A.: The Effect of Anterior Lobe Administered Intraperitoneally upon Growth and Maturity of the Oestrous Cycles of the Rat, Anat. Rec. **21**:62-63, 1921.

stance by injecting their preparation intraperitoneally into rats daily for several days. This treatment resulted in the growth of the animals to twice the size of the untreated controls. Aschner demonstrated that immature puppies remained dwarfed and sexually infantile after hypophysectomy (Cushing [27]). Any condition which causes a hyposecretory state of the eosinophilic cell of the anterior lobe of the hypophysis may result in a functional deficiency in growth. Evidence favors the conception that the anterior lobe secretes directly into the systemic circulation (Rioch [28]). Any disturbance of the blood supply which is peculiar to the gland (Wislocki [29]), like actual pressure changes in the glandular tissue from tumor growth, may produce dyspituitarism.

The hormone of the thyroid gland is essential to the growing child in that it markedly influences the rate of growth and differentiation of tissues, the rate of energy exchange and the metabolism. Whereas the growth-stimulating hormone of the pituitary seems to stimulate the increase in mass, the thyroid secretion is necessary to the proper differentiation and specialization of tissues. Because of their influence on the metabolism of calcium and phosphorus, the parathyroid glands are also indispensable to growth.

The type of dwarfism resulting from endocrine dysfunction has varied. No satisfactory explanation for the different types has been found. It may be that in the absence of pituitary function, or in apituitarism, one type results, while dyspituitarism, or disordered pituitary function, tending toward diminished activity, produces another type. The features of both the Lorain and the Fröhlich type of dwarfism have been described (Worster-Drought, Dickson and Archer [22]; Lorain [30]; Weber [31]; Lurie [32]; Cushing [33]). The person with the Lorain type is slender, delicate, asthenic and fragile in appearance and often has a senile look. Perhaps such persons are described best as adults in small

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27. Cushing, H.: Dyspituitarism Twenty Years Later, with Special Consideration of the Pituitary Adenomas, Arch. Int. Med. **51**:487-557 (April) 1933.

28. Rioch, D. M.: Paths of Secretion from the Hypophysis, A. Research Nerv. & Ment. Dis., Proc. (1936) **17**:157-171, 1938.

29. Wislocki, G. B.: The Vascular Supply of the Hypophysis Cerebri of the Rhesus Monkey and Man, A. Research Nerv. & Ment. Dis., Proc. (1936) **17**: 48-68, 1938.

30. Lorain, P. J.: Preface, in Faneau de la Cour, F. V.: Du féminisme et de l'infantalisme chez les tuberculeux, Thesis, Paris, no. 1, 1871.

31. Weber, F. P.: Ateleiotic Dwarfism, Internat. Clin. **2**:91, 1921.

32. Lurie, L. A.: Pituitary Disturbances in Relation to Personality, A. Research Nerv. & Ment. Dis., Proc. (1936) **17**:547-560, 1938.

33. Cushing, H.: The Pituitary Body and Its Disorders, Philadelphia, J. B. Lippincott Company, 1912.

molds, in whom an arrest of development has affected the mass of the body rather than any specific organ. Such dwarfism is not true nanism, or infantilism in which certain morphologic characteristics of infancy are retained. The skin is thin and the hair fine. Persons with this disease have aggressive, dominant personalities and are mentally alert.

The Fröhlich type of dwarfism is the usual and more commonly known. It is characterized by eunuchoid obesity, alteration of the secondary sex characteristics, change in bodily growth and metabolic disturbances. There is an enormous overgrowth of the subcutaneous fat, which is deposited more or less generally but tends to be placed so as to exaggerate the female outline of the figure. Thus, males show a relatively greater thickening of the buttocks and thighs and a subcutaneous deposit in the breasts. The genitals are hypoplastic. Menstruation, facultas coeundi and libido are lost if the disease sets in after puberty and fail to appear if the syndrome is present before puberty. Males lose facial and pubic hair or have a feminine distribution of pubic hair. In addition, there may be polyuria, polydipsia and increased sugar tolerance. Such symptoms as optic atrophy and palsies of other cranial nerves, headache and somnolence may be the same as those associated with any other tumor of the pituitary. Patients with this disease have submissive, compliant personalities; they lack aggressiveness and are timid and phlegmatic; their mental retardation is more apparent than real; they have a longer reaction time than normal persons.

Basal metabolism, when disturbed, is usually subnormal, regardless of the type of lesion causing the hypophysial dysfunction. Therefore a subnormal metabolic rate has no significance in differentiating between tumors of the craniopharyngeal duct, such as adamantinomas, and tumors of the pituitary body, such as adenomas. The low basal metabolic rate may not be accompanied by any striking nutritional disturbance (Frazier [5b]). This may be due to secondary disturbance of thyroid function. The results of dextrose tolerance tests in the case reported were similar to those obtained by Beckmann and Kubie [6]; there were a slow rise of the blood sugar to a high level and a slow return to normal. Davidoff and Cushing [34] emphasized the high sugar tolerance. There is evidence that the anterior lobe of the pituitary and the adrenal medulla work together in balancing pancreatic activity. The adrenals respond normally to insulin hypoglycemia by liberating epinephrine into the blood stream, but in the absence of the pituitary the epinephrine is unable to raise the low blood sugar level in spite of the presence of an ample

34. Davidoff, L. M., and Cushing, H.: Studies in Acromegaly: The Disturbances in Carbohydrate Metabolism, Arch. Int. Med. **39**:751-779 (June) 1927.

reserve of liver glycogen (Cope and Marks [35]). Houssay and Biasotti [36] and Collip [37] have also pointed out the interdependence of the pancreas and the anterior lobe of the pituitary gland.

ROENTGENOLOGIC OBSERVATIONS

Roentgen examination may show that the flat bones of the skull have been thinned by pressure of the brain; particularly over the convolutions the bones may have a mottled appearance, designated as convolutional atrophy, which indicates prolonged intracranial hypertension. Separation of the cranial sutures is not uncommon. Neither of these changes in itself is necessarily indicative of tumor, but when associated with other roentgen evidence and clinical data such observations aid in the diagnosis of intracranial lesions producing hypertension.

Local changes about the sella turcica and the sphenoid sinus are of the greatest value in the diagnosis of hypophysial and suprasellar lesions. McKenzie and Sosman [38] found that in 76 per cent of the cases they studied the sella turcica was abnormal. Certain factors relating to the normal development of the parasellar part of the skull should be kept in mind. In the young child the sphenoid sinus is developed only in the presphenoid area and but slightly in the postsphenoid region. At this time the floor of the sella is formed by the solid structure of the basisphenoid bone, and the posterior limit of the sinus is just anterior to and below the anterior wall of the sella. Roentgenograms made during this period will show the dense shadow of the basisphenoid bone below the sella and the small sphenoid air space anterior to it. With increase in age and further development of the sinus, the bony structure of the basisphenoid bone gives way to the enlarging air cells, and, according to the extent of development, the sella is partially or completely undermined by the sphenoid air space, which may extend to the tips of the posterior clinoid processes, leaving only the shadow of a thin bony plate.

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35. Cope, O., and Marks, H. P.: Further Experiments on the Relation of the Pituitary Gland to the Action of Insulin and Adrenalin, J. Physiol. **83**:157-176 (Dec. 31) 1934.

36. Houssay, B. A.: The Hypophysis and Metabolism, New England J. Med. **214**:961-986 (May 14) 1936. Houssay, B. A., and Biasotti, A.: The Hypophysis, Carbohydrate Metabolism and Diabetes, Endocrinology **15**:511-523 (Nov.-Dec.) 1931.

37. Collip, J. B.: Diabetogenic, Thyrotropic, Adrenotropic and Parathyrotropic Factors of the Pituitary, J. A. M. A. **104**:827-832 (March 9) 1935.

38. McKenzie, K. G., and Sosman, M. C.: The Roentgenological Diagnosis of Craniopharyngeal Pouch Tumors, Am. J. Roentgenol. **11**:171-176 (Feb.) 1924.

Gordon and Bell [39] have demonstrated that there is a marked change in the height and the length of the sella turcica with age and that there is a range of values for those measurements among subjects of any given age. There is a comparatively rapid increase in the height and the length of the sella during the first two years of life and a gradual, yet irregular, increase from then to the age of 12. There is apparently no relation between the size of the head and the size of the sella. Flat and saucer-shaped sellas are observed practically only during the first three years of life. Circular and oval sellas are found in persons of all ages, the circular type predominating in children and the oval in adults. Since the size and the contour of the normal sella vary greatly, it is difficult to recognize early pathologic changes in roentgenograms.

Since the location of the congenital anlages determines where the tumors arising from them are located, the lesion may be anywhere along the hypophysial stalk and therefore may be primarily intrasellar or entirely extrasellar. It is possible for an intrasellar tumor to break through the aperture of the tentorium of the sella early in its development and thus grow above the sella and lie chiefly suprasellar. Most often, however, the diaphragma sellae firmly covers the outlet of the pituitary fossa, and the typical changes produced by the tumor growing within its boundaries distinguish the lesion from a suprasellar growth.

With the intrasellar tumor, the sella becomes enlarged as the growth exerts pressure. The enlargement tends to be uniform and circular and takes place at the expense of the floor, which may be eroded and produce a pouching into the sphenoid sinus or may even be totally destroyed. Varying degrees of erosion of the dorsum sellae occur. The progressive changes usually can be seen on successive roentgen examinations. First a concavity is produced on the anterior surface of the dorsum sellae; later a straight and narrow appearance results from the increasing pressure, and finally the dorsum sellae is pushed backward and may entirely disappear. The anterior clinoid processes are usually not affected until late; they become eroded from below and behind, with the formation of short blunt processes. It is by virtue of its location that an intrasellar tumor is unable to produce an increase of intracranial pressure until it has reached considerable size. Consequently, the presence of a uniform circular enlargement of the sella, with or without erosion and distention of the floor, with thinning of the dorsum sellae and without evidence of pressure changes in the rest of the skull, except with an advanced lesion, is pathognomonic of intrasellar tumor (Camp [40]).

39. Gordon, M. B., and Bell, A. L. L.: A Roentgenographic Study of the Sella Turcica in Normal Children, New York State J. Med. **22**:54-58 (Feb.) 1922.

40. Camp, J. D.: The Normal and Pathological Anatomy of the Sella Turcica as Revealed by Roentgenograms, Am. J. Roentgenol. **12**:143-156 (Aug.) 1924.

It must be remembered that any lesion which produces an increase of intracranial pressure by virtue of its size or its ability to obstruct the ventricular system of the brain will produce corresponding changes in the outline of the sella purely as the result of the transmitted pressure. These changes appear simultaneously with the other pressure changes in the skull and consistently tend to widen and flatten the pituitary fossa. Destruction of the posterior clinoid processes is frequent. This is perhaps due to their erect position and central location. They are eroded from above and become shortened and pointed. The outlet of the fossa becomes widened, and the depth is diminished rather than increased. Since the development of the sphenoid bone has not been completed, the posterior clinoid processes in children are often inconspicuous; there may be only a rounded upper border of the thick dorsum sellae. The slight difference in the amount of destruction of the clinoid processes produced by a unilateral, instead of a bilateral, tumor is indistinguishable in the roentgenogram. Regardless of the cause of the increased intracranial pressure, the amount of destruction demonstrated in the anatomic specimens in Camp's cases was always greater than that which had been visualized in the roentgenograms. But Camp found that measurements for the sella made from the roentgenogram coincided almost exactly with those obtained by direct examination of the anatomic specimens and the wax models of the pituitary fossa.

An uncalcified tumor does not cast a shadow in the roentgenogram unless it has invaded the accessory sinuses. Possible exceptions are hypophysial lesions, which are viewed against the dark temporal fossa. Suprasellar calcification is the most significant observation in roentgen examination of tumors of the hypophysial stalk in children. It has been present in 70 to 85 per cent of the cases of such tumors. Such localized nodular calcification occurs in hardly any other condition involving the vicinity of the sella (Duffy[3]). Since the calcification is usually nodular and occurs chiefly in the solid parts of the tumor, it is less apt to be noticed in the walls of the cysts. It may be delicate and spongy and varies in extent from a few pinpoint specks to a mass 8 cm. in diameter. It is usually in the midline, either directly above the sella or over the anterior clinoid processes. Often the detail of calcification above the sella is lost in the shadow of the cranial vault. Films should be exposed and developed so that the soft tissues are obliterated and the roentgenogram looks moderately overexposed.

Practically all tumors of the brain either directly or indirectly affect some part of the ventricular system (Dandy[41]). Therefore ventriculographic examination may be valuable in the localization of

41. Dandy, W. E.: Localization or Elimination of Cerebral Tumors by Ventriculography, Surg., Gynec. & Obst. **30**:329-342 (April) 1920.

obscure tumors. A ventriculogram will, in many cases, at once tell whether the tumor is cerebral or cerebellar. In cases of the latter type of tumor an internal hydrocephalus will be evidenced by the symmetrically enlarged lateral ventricles. A small ventricle is presumptive, though not absolute, evidence of a cerebral tumor as against a tumor of the cerebellum or of the brain stem.

During the course of growth and development of the hand and wrist, over a score of epiphyses make their appearance in both the long and the short bones. There is sufficient difference between the times of appearance and union of the several epiphyses to make roentgenograms of this region especially valuable. The epiphyses and centers of ossification furnish by their size and modeling information on the stage of osseous growth.

Differential Diagnosis.—There are nearly three dozen different dietary substances which the growing child must have if he is to grow normally. One half of the total growth of the human being is attained during the first three years of life. Malnutrition should therefore be strongly suspected as the causative factor of any child's stunted growth. It has recently been pointed out by Farquharson and Hyland,[42] Ross,[43] Bruckner, Wies and Lavietes [44] and Sheldon and Young [45] that it is difficult to differentiate anorexia nervosa from pituitary cachexia. Anorexia nervosa occurs chiefly among adolescent girls after some prolonged emotional conflict, either avowed or concealed, which leads to loss of appetite. The intake of food becomes grossly insufficient, and there is marked loss of weight. Many of the symptoms referable to the endocrine glands, such as emaciation, amenorrhea, subnormal temperature, low pulse and blood pressure and altered sugar tolerance, may result from this morbid aversion to eating and make differential diagnosis difficult. Forced feeding and psychologic management usually cure patients with this disorder.

The emaciation of the patient in the case reported here was so marked that her illness was thought to be cachexia hypophyseopriva, or Simmonds' disease. If a broad point of view is taken and it is deemed possible for a child to have the condition, then it is believed that in this case there were sufficient clinical and necropsy data to justify the diagnosis.

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42. Farquharson, R. F., and Hyland, H. H.: Anorexia Nervosa: A Metabolic Disorder of Psychologic Origin, J. A. M. A. **111**:1085-1092 (Sept. 17) 1938.

43. Ross, W. C.: Anorexia Nervosa with Special Reference to the Carbohydrate Metabolism, Lancet **1**:1041-1045 (May 7) 1938.

44. Bruckner, W. J.; Wies, C. H., and Lavietes, P. H.: Anorexia Nervosa and Pituitary Cachexia, Am. J. M. Sc. **196**:663-673 (Nov.) 1938.

45. Sheldon, J. H., and Young, F.: On the Carbohydrate Metabolism in Anorexia Nervosa, Lancet **1**:257-259 (Jan. 29) 1938.

Smith [16] showed experimentally that complete inhibition of growth could be produced in young rats by ablation of the anterior lobe of the hypophysis. The invariability of these changes seems to verify the original contention of Simmonds [46] that the clinical syndrome accompanying the destruction of the anterior lobe of the hypophysis always assumed a definite form, described by him as hypophysial cachexia, regardless of the nature of the process causing the change. Calder [47] and Silver [48] have reviewed the literature on Simmonds' disease.

Since the patient in the case reported here was a child, one could not expect her to show the classic symptoms manifested by adults. She was too young to have any of the menstrual or sexual changes. Likewise, secondary changes in the skin could not be demonstrated. There was no falling of hair of the scalp. Her hair was long, shaggy and fine textured. Marked anorexia was present, and cachexia was the most outstanding clinical feature. Mahoney [49] has demonstrated that cachexia can be prevented in the hypophysectomized experimental animal by a high intake of carbohydrate. The question arises whether the almost forced high calory diet was effective in maintaining the child's weight at a constant level when there was a previous history of rapid loss of weight before coming under medical care. No change in weight after thyroid medication was demonstrated (Wahlberg [50]). The child showed no mental lethargy or psychic symptoms. She was somnolent at intervals but never comatose. She was usually sharply alert and was never irrational. She had the typical desire to rest all the time and tired easily, always being worn out at the end of the day. She complained of headaches and periodic vomiting. Her teeth were poor. Her temperature tended to be subnormal, and her blood pressure was low. One wonders whether if this child had been older she would have had the typical changes in sexual characteristics and menstruation.

Lignac [51] reported several cases of a renal condition occurring in infants and children in which there were later shown stunted growth

46. Simmonds, M.: Ueber Kachexie hypophysären Ursprungs, Deutsche med. Wchnschr. **42**:190, 1916.

47. Calder, R. M.: Anterior Pituitary Insufficiency (Simmonds' Disease), Bull. Johns Hopkins Hosp. **50**:87-114 (Feb.) 1932.

48. Silver, S.: Simmonds' Disease (Cachexia Hypophyseopriva): Report of Case with Postmortem Observations and a Review of the Literature, Arch. Int. Med. **51**:175-194 (Feb.) 1933.

49. Mahoney, W.: Hypoglycemia Hypophysiopriva, Am. J. Physiol. **109**:475-482 (Sept.) 1934.

50. Wahlberg, J.: Hypophyseothyrogenic Adiposity and Emaciation, J. A. M. A. **106**:1968-1970 (June 6) 1936.

51. Lignac, G. O. E.: A Syndrome Consisting of Affections of the Kidney, Stunted Growth, Rickets, and Disturbed Cystine Metabolism, Am. J. M. Sc. **196**:542-547 (Oct.) 1938.

and development, fully developed rickets and a disturbance of cystine metabolism, while the normal proportions of the skeleton remained unchanged. There was cystinuria, and examination showed crystalline deposits of cystine in different organs, which were believed to be due to inability of the patient to assimilate the substance and inability to excrete it completely because of the impaired renal function.

The acute infectious diseases of childhood apparently exert no permanent unfavorable influence on the rate of growth. Chronic infections, especially chronic osteomyelitis, do exert unfavorable influences on growth, and when they occur during what would otherwise be periods of rapid growth, they may leave the body stunted, in which case anamnesis is important for diagnosis. In cases of cachexia from wasting diseases, such as tuberculosis, the patients are usually ill, complain of weakness and fatigue and often have physical signs before marked emaciation has occurred. Juvenile patients with diabetes often have hyperactivity of the pituitary gland in the prediabetic stage, followed by hypopituitarism later in the course of the disease (White [52]). This disturbed hormonal balance, together with the nutritional inadequacies and metabolic disturbances incident to diabetes mellitus, undoubtedly contributes to the inability of some children with diabetes to maintain a normal rate of growth. Emaciation is also often a late symptom in Addison's disease. The characteristic weakness, pigmentation and crises of nausea differentiate this condition, which is not common, but does occur, in childhood.

In cases of vomiting such causes as disturbances of the gastrointestinal tract and parenteral infections have to be ruled out. Lead poisoning with peripheral neuritis and bilateral choking of the optic disks is not uncommon in children. The lead line of the gums and the stippling of the red blood cells help to determine this diagnosis. Thrombosis of the dural sinuses, chronic inflammatory conditions of the brain, optic neuritis, the retinitis of hypertensive cardiovascular-renal disease and hemorrhagic neuroretinitis may present a picture identical with that of choking of the optic disks resulting from a tumor of the brain (Stough [53]).

Tumors of the brain are not as uncommon in childhood as the general practitioner comes to believe. In fact, a median tumor of the cerebellum is so common a lesion in preadolescence that when a child has unexplained vomiting, shows possible enlargement of the head, has irregular bouts of headache or gives a story of periodic unsteadiness it is well to be on guard and to examine the eyegrounds every week or

52. White, P.: Endocrine Manifestations in Juvenile Diabetes, Arch. Int. Med. **63**:39-53 (Jan.) 1939.

53. Stough, J. T.: Choking of the Optic Disks in Diseases Other Than Tumor of the Brain, Arch. Ophth. **8**:821-830 (Dec.) 1932.

two. Any persistent or repeated headache in a child should arouse the suspicion of tumor, and the head should be periodically measured and percussed, especially after the headaches have ceased (Cushing [2]). One should not wait until the vision has failed before examining the eyes. Ophthalmoscopic examinations should be as routine as the inspection of the ear drums. Frequent charting of the visual fields is a far surer guide to the patient's condition than repeated roentgen examinations of the sella turcica (de Schweinitz [54]). At puberty, any child showing retardation of growth, particularly if he has attacks of transitory blindness, should be studied immediately for intracranial changes.

The localization of an intracranial tumor is often as difficult as determining that such a lesion is present. That neoplasms of the brain may give rise to disorders of parts of that organ far distant from the actual site of the growth, through distortion, edema, pressure, internal hydrocephalus or other means, is well known. Secondary enlargement of the sella turcica produced by distant lesions may be mistaken for the enlargement caused by a local tumor. There may be more or less pronounced palsies of the cranial nerves due to their compression or distortion as the configuration of the brain is altered by new growths, and thus false localizing signs may be produced (Cushing [55]). The strange fact that the sella turcica was not more deformed in the case presented here was a misleading sign. It showed no more deformation than sometimes occurs from a general increase of intracranial pressure, particularly the pressure produced by tumors of the posterior cranial fossa, which dilates the third ventricle by the pressure exerted on the fourth ventricle or the aqueduct of Sylvius. Such secondary hydrocephalus may cause many of the hypophysial and hypothalamic symptoms of tumors of the hypophysial stalk, even in cases in which the cerebellar symptoms are slight. Likewise, but less commonly, the reverse may occur; namely, suprasellar tumors may disturb the functioning of the cerebellum. The differential diagnosis is sometimes impossible, and perhaps the most frequent diagnostic error consists in mistaking tumors of the third ventricle for cerebellar tumors (Bailey [56]), especially in the cases of children. The main source of difficulty in the differential diagnosis of supratentorial and infratentorial tumors lies in the equilibratory disturbances which both types of tumor may cause. Either direct involvement of the red nuclei or of the cerebrocerebellar connections or the indirect effects of the hypertension caused by dilatation of the third ven-

54. de Schweinitz, G. E.: Ocular Aspects of Pituitary Disorders: A Review of Bowman Lecture, Brit. M. J. **1**:816 (May 12) 1923.

55. Cushing, H.: Anosmia and Sellar Distension as Misleading Signs in Localizing of a Cerebral Tumor, J. Nerv. & Ment. Dis. **44**:415-423 (Nov.) 1916.

56. Bailey, P.: Concerning the Cerebellar Symptoms Produced by Suprasellar Tumors, Arch. Neurol. & Psychiat. **11**:137-150 (Feb.) 1924.

tricle may produce ataxia, which is always cerebellar in type (Weisenburg,[57] Muskens [58]). The efferent pathways of the cerebellum located in the superior cerebellar peduncles are most often disturbed by the pressure as the brain stem herniates through the aperture of the tentorium cerebelli. Since these symptoms are combined with marked increase of intracranial pressure, which always ensues from a tumor of the posterior cranial fossa, the misleading character of the picture can readily be appreciated. A good history usually reveals sufficient clinical data to show which manifestations have developed secondarily to pressure. It will be remembered that among children the incidence of cerebellar tumors is twice that of cerebral lesions, while among adults the incidence is one-fifth that of cerebral lesions. Dyssynergia, hypermetria, hypotonia, tremor and other symptoms of derangement of the function of the cerebellum are usually present from the onset in cases of true cerebellar lesions. In cases of supratentorial lesions the secondary cerebellar symptoms appear late in the clinical course of the disease (Critchley [59]). Ventriculographic examination may be of much value in localizing the lesion.

Even when a localizing diagnosis of parasellar tumor has been made, it is still necessary to make a pathologic diagnosis. This is not easy and is often impossible except by direct examination of tissue. For differentiating tumors in the parasellar region, Frazier [60] has presented much valuable information.

Tumors of the hypophysial stalk produce symptoms of obstructive hydrocephalus, such as headache, vomiting and papilledema, pressure on the chiasm, primary optic atrophy, distortions of the visual fields, structural alterations about the sella turcica and endocrine disturbances. Seventy per cent of such tumors occur in patients under 20 years of age. The histologic picture is typical, the basilar layer of ameloblastic cells being characteristic. The tumors are prone to undergo cystic degeneration, with numerous areas of calcification; therefore they show as shadows on the roentgenogram. Eighty-five per cent of the tumors of Rathke's pouch can be positively diagnosed by roentgen examination (McKenzie and Sosman [38]). Because a suprasellar tumor is so situated that it can easily interfere with the blood vessels and the infundibulum of the pituitary gland and thus impede the elimination of pituitary secre-

57. Weisenburg, T. H.: Tumors of the Third Ventricle with the Establishment of a Symptom Complex, Brain **33**:236-260, 1910.

58. Muskens, L. J. J.: The Central Connections of the Vestibular Nuclei with the Corpus Striatum and Their Significance for Ocular Movements and for Locomotion, Brain **45**:454-478 (Dec.) 1922.

59. Critchley, M.: The Diagnosis of Cerebellar Tumours in Children, Brit. J. Child. Dis. **23**:165-177 (July-Sept.) 1926.

60. Frazier, C. H.: A Review, Clinical and Pathological, of Parahypophyseal Lesions, Surg., Gynec. & Obst. **62**:1 (Jan.); 158 (Feb.) 1936.

tion, such a lesion is frequently associated with hypopituitary or dyspituitary symptoms, in contradistinction to the symptoms of pituitary hyperactivity which usually accompany a tumor of intrasellar origin. Seventy per cent of the pituitary tumors associated with Fröhlich's syndrome are located in the craniopharyngeal pouch (Jackson [61]).

The endocrine glands have an inherent interdependence and interaction. Destruction of the hypophysis or disturbance in its function may produce secondary changes in other glands of the body, and a complicated clinical picture may result. Symptoms of myxedema, signs of adrenal failure with hypotension, pigmentation and hypoglycemia, adynamia, evidences of parathyroid tetany and pancreatic glycosuria may all be in evidence. These signs and symptoms tend to substantiate the conclusions of such authors as Claud and Gougerot and Falta that pluriglandular involvement is present. Weinstein [62] and Crile, Turner and McCullagh [63] have discussed such multiglandular syndromes.

TREATMENT

It is not conceivable that such neoplasms as tumors of the hypophysial stalk disappear spontaneously or are cured or even benefited by any form of medical therapy (Dandy [41]). Attempts at medical treatment only cause delay, which is disastrous to the patient. Numerous reports have been made on the results of clinical application of various preparations of the active principles of the anterior lobe of the pituitary and of whole gland extracts in cases of dwarfism, infantilism and pituitary cachexia, and in more than a few cases remarkable improvement ensued (Engelbach [64]; Schaefer [65]; Shelton, Cavanaugh and Evans [66]; Evans [67]; Schaefer and Strickroot [68]; Taylor [69]). That

61. Jackson, H.: Craniopharyngeal Duct Tumors, J. A. M. A. **64**:1082 (April 8) 1916.

62. Weinstein, A.: Multiglandular Syndromes Resembling Simmonds' Disease, with Case Report, Am. J. M. Sc. **189**:245-253 (Feb.) 1935.

63. Crile, G.; Turner, H., and McCullagh, E. P.: Polyglandular Disease, New York State J. Med. **36**:475-484 (April 1) 1936.

64. Engelbach, W.: The Growth Hormone: Report of a Case of Juvenile Hypopituitarism Treated with Evans' Growth Hormone, Endocrinology **16**:1-19 (Jan.-Feb.) 1932.

65. Schaefer, R. L.: Endocrine Dwarfism, Endocrinology **20**:64-71 (Jan.) 1936.

66. Shelton, E. K.; Cavanaugh, L. A., and Evans, H. M.: Hypophyseal Infantilism: Treatment with Anterior Hypophyseal Extract, Am. J. Dis. Child. **47**:719-736 (April) 1934.

67. Evans, H. M.: Clinical Manifestations of Dysfunction of the Anterior Pituitary, J. A. M. A. **104**:464-472 (Feb. 9) 1935.

68. Schaefer, R. L., and Strickroot, F. L.: Endocrine Dwarfism, Endocrinology **26**:599-608 (April) 1940.

69. Taylor, N. M.: Pituitary Dwarfism: Treatment with Growth Hormone, Endocrinology **22**:707-715, 1938.

there has been a certain amount of success with this form of treatment is evident, but it has been suggested frequently that the diagnosis and the conclusions regarding the results of medical treatment be accepted with caution. In few, if any, of the cases in which this form of therapy has been considered successful has autopsy revealed a tumor of the hypophysial stalk. On the other hand, substitution therapy may be of value after the tumor has been removed or a palliative decompression has been carried out. The excessive adiposity has generally been lessened if operative procedures have been supplemented by the administration of whole gland preparations. Marked change in growth has not yet been produced, and sexual development has been little affected. Improvement has been reported to have followed the administration of extract of the anterior lobe, especially in improving motor weakness and prostration (Frazier [5b]). The patients have been able to be up and about, and the somnolence and chills have decreased and the blood pressure increased. In the practical management in such cases, the reduction in the activity of the thyroid occurring concomitantly with the pituitary dwarfism should not be disregarded. It should be remembered that attempts to stimulate the development of the secondary sex characteristics by treatment with potent preparations containing the gonad-stimulating factor may hasten epiphysial closure and defeat the purpose of treatment with the growth-promoting factor.

Neurosurgeons have confessed that tumors of the hypophysial stalk often are more easily diagnosed than treated. Solid tumors are almost always so adherent to the structures at the base of the brain that total removal of the lesion is impossible without serious injury to these important structures. Partial removal may be followed by symptoms of severe, and even fatal, toxicity. In at least 20 to 25 per cent of the cases, hyperthermia and other acute effects of the collapse of the hypothalamic region are manifested (Bailey [1]). Such tumors are much more difficult to deal with than cysts, which can be emptied and the cyst wall removed. In cases with hypopituitary symptoms, especially low blood pressure, which is present in so many cases of tumors of the hypophysial stalk, greater risk is attached to surgical intervention than in those in which the blood pressure and pituitary function are normal. Consequently, the operative mortality is high and the prospect of substantial and lasting benefit small.

Usually the lesions are in an advanced stage when the patient first seeks relief; 90 per cent of the patients have failing vision and 24 per cent are totally blind in at least one eye before the nature of the lesion is revealed (Frazier [70]). Then the pressing problem from the standpoint of treatment is the immediate relief of intracranial pressure. Gen-

70. Frazier, C. H.: Lesions of the Hypophysis from the Viewpoint of the Surgeon, Surg., Gynec. & Obst. **17**:724-736, 1913.

erally speaking, a subtemporal decompression accomplishes little when there is obstructive hydrocephalus, for the relief from pressure is only temporary. A suboccipital decompression is extremely dangerous when the lesion is in the supratentorial cavity (Dandy [41]). In cases of progressive blindness or when it is evident that the tumor immediately jeopardizes the life of the patient, many surgeons feel justified in attempting to remove the causative lesion, regardless of the operative risk and the possible postoperative morbidity.

Four main methods of approach to pituitary and parasellar tumors have been used, namely, Cushing's submucous septal approach, Frazier's fronto-orbital method, Horsley's temporal method and Schloffer's nasal operation. The various deviations from these have been reviewed by Cope.[71] The nasal operation was made popular by Kanavel,[72] Halstead [73] and Cushing.[74] In this method the floor of the sella turcica was reached by an endonasal route by resection of a portion of the septum and the vomer and entering the sphenoid cells and then the floor of the pituitary fossa. This route was advocated especially when there had already been a spontaneous decompression of the tumor growth by erosion of the floor of the sella turcica into the sphenoid sinus. The growth was removed as largely as possible by suitable long-handled scoops or by suction. At one time this approach was advocated for use in all cases of cysts and of all tumors causing enlargement of the sella. Many surgeons have expressed the opinion that this method is not practical for the removal of tumors lying in juxtaposition to the hypophysis and hence giving rise to hypophysial symptoms. All of the tumor mass cannot be removed when it has extended widely outside the sella turcica. The proportion of tissue actually removed is always indefinite because of the limited exposure, and it is probably only rarely that anything like even a subtotal evacuation has been accomplished (Horrax [75]). Gibson [76] has described the topography of the hypophysis cerebri and some of the variations encountered in the transsphenoid approach. The intrasphenoid septum is variable in its position and not infrequently may be so much to one side that if it is taken for a guide

71. Cope, V. Z.: The Pituitary Fossa and the Methods of Surgical Approach Thereto, Brit. J. Surg. **4**:107-144 (July) 1916.

72. Kanavel, A. B.: The Removal of Tumors of the Pituitary Body by an Intranasal Route, J. A. M. A. **53**:1704-1707 (Nov. 20) 1909.

73. Halstead, A. E.: Remarks on the Operative Treatment of Tumors of the Hypophysis, Surg., Gynec. & Obst. **10**:494-502, 1910.

74. Cushing, H.: Surgical Experiences with Pituitary Disorders, J. A. M. A. **63**:1515-1525 (Oct. 31) 1914.

75. Horrax, G.: The Surgical Treatment of Pituitary Tumors, A. Research Nerv. & Ment. Dis., Proc. (1936) **17**:665-682, 1938.

76. Gibson, W. S.: The Topography of the Hypophysis Cerebri, Surg., Gynec. & Obst. **15**:199-205, 1912.

in the intranasal operation one of the cavernous sinuses is likely to be opened instead of the pituitary fossa. Almost all neurosurgeons have now abandoned the transsphenoid operation in favor of some form of frontal intracranial route (Frazier,[77] Heuer,[78] Cushing,[79] Dandy[80]). An osteoplastic flap is placed far enough anteriorly for the frontal lobe, usually the right, to be retracted easily and the chiasmal region exposed.

In early days the intracranial operation carried a mortality of approximately 30 to 40 per cent (Horrax[75]). Cushing's transfrontal operative mortality was 6.2 per cent. He reported 149 cases in which the transsphenoid route was used and 19 in which the approach was transfrontal, with a mortality of 9 and 5, respectively (Cushing[81]). Whereas 37 per cent of the patients after transsphenoid operations and 42 per cent after transfrontal operations showed considerable or marked improvement in vision, only 9 per cent of the transsphenoid operations, in contrast to 21 per cent of the transfrontal operations, were followed by restoration of the visual fields and acuity essentially to normal.

When operative measures offer relief from pressure there is usually a disappearance of such symptoms as vomiting, headache and visual disturbances. The recession of the visual defects takes place in a sequence, the reverse of the stages characterizing an advancing process. The restoration of sight usually takes two to eight weeks, a relative paracentral scotoma often persisting. Restoration of normal peripheries of the fields is possible even when the process has advanced to, or beyond, the typical half-vision stage. Some vision may be regained even after blindness has occurred provided it has not been of too long duration. Therefore the so-called primary optic atrophy does not always represent an actual anatomic degeneration so much as a physiologic block to the transmission of visual impulses. The ocular signs are uniformly bettered unless complete nerve atrophy is present.

Most of the irradiation therapy to tumors in the parasellar region has been given with effect in cases of tumors of the pituitary gland itself. The adenomas respond well, and in many instances irradiation has caused marked diminution in the size and retardation of the growth of the tumor mass. The chromophile-acidophile adenomas regress further and more rapidly than those which are chromophobe. The duration of

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77. Frazier, C. H.: An Approach to the Hypophysis Through the Anterior Cranial Fossa, Ann. Surg. **57**:145-150 (Feb.) 1913; footnote 70.

78. Heuer, G. J.: Surgical Experiences with and Intracranial Approach to Chiasmal Lesions, Arch. Surg. **1**:368-381 (Sept.) 1920.

79. Cushing, H.: Intracranial Tumors, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

80. Dandy, W. E., in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1932, vol. 12, chap. 1.

81. Cushing, H.: Series of Intracranial Tumors and Conditions Simulating Them, Arch. Neurol. & Psychiat. **10**:605-668 (Dec.) 1923.

beneficial results may be a number of years (Dyke and Hare [82]). Some of the other tumors, such as the meningiomas, the acoustic neuromas or the tumors of Rathke's pouch, which may be more or less positively diagnosed previous to operation, do not react favorably to roentgen treatment. Irradiation will have less influence on a lesion which is already cystic. A pathologic, as well as a localizing, diagnosis is necessary, then, for proper roentgen therapy (Bailey [83]). Since in a large percentage of cases an exact pathologic diagnosis cannot be made without operation, an exploration should always precede roentgen therapy, except possibly in cases of adenomas of the pituitary body. But even in those cases repeated examinations of the visual field and investigations of the condition of the optic disks and the rapidity of failure of vision should determine whether roentgen therapy or surgical intervention should be employed. All observers agree that in every case in which treatment with roentgen rays is employed the progress of the patient must be carefully checked by frequent perimetric examinations and that if vision continues to decrease operative intervention is indicated (Dott, Bailey and Cushing [84]; Pfahler and Spackman [85]; Dyke and Hare [82]; Towne [86]; Bailey [83]; Frazier [5a]).

On the basis of results, surgical treatment seems to be more effective than roentgen therapy. In Cushing's series of patients who underwent operation, 21 per cent had restoration of visual fields and acuity of vision to normal and an additional 42 per cent showed considerable or marked improvement (Cushing [81]). In the series of Hare and Dyke,[87] which consisted of patients given roentgen therapy, only 5 per cent had return of vision to normal, 25 per cent showed improvement and another 25 per cent had further diminution in vision. The latter authors pointed out that the symptoms of headache and drowsiness were relieved in 75 per cent of the cases in which roentgen therapy was employed. These symptoms, then, can still be influenced by irradiation when irreparable damage to the optic fibers has made improvement in vision impossible. Vision is by far the most important function to save. Whenever a tumor of the brain substance cannot be removed, or is removed only

82. Dyke, C. G., and Hare, C. C.: Roentgen Therapy of Pituitary Tumors, A. Research Nerv. & Ment. Dis., Proc. (1936) **17**:651-664, 1938.

83. Bailey, P.: The Results of Roentgen Therapy on Brain Tumors, Am. J. Roentgenol. **13**:48-53 (Jan.) 1925.

84. Dott, N. M.; Bailey, P., and Cushing, H.: A Consideration of the Hypophyseal Adenomata, Brit. J. Surg. **13**:314-365 (Oct.) 1925.

85. Pfahler, G. E., and Spackman, E. W.: Roentgen Therapy in Pituitary Tumors, Am. J. Ophth. **14**:796-807 (Aug.) 1931.

86. Towne, E. B.: Treatment of Pituitary Tumors: The Role of the Roentgen Ray and of Surgery Therein, Ann. Surg. **91**:29-36 (Jan.) 1930.

87. Hare, C. C., and Dyke, C. G.: Roentgen Therapy of Pituitary Tumors: Report of Twenty Cases, Arch. Ophth. **10**:202-225 (Aug.) 1933.

in part, it should be subjected to as intensive roentgen treatment as is compatible with the well-being of the surrounding brain tissue, even though it is known that the effort to destroy the tumor or to prevent its recurrence in some cases will be futile (Bailey [83]).

SUMMARY

A report of the case of a 6½ year old child who had an adamantinoma of the craniopharyngeal duct with the resultant manifestations of marked cachexia and the Lorain type of dyspituitarism is presented with the observations made at autopsy.

The difficulties in the differential diagnosis of this condition are emphasized, especially in relation to (1) the general features of stunted growth and cachexia, (2) the existence of an intracranial tumor, (3) the localization of the tumor mass in the brain and (4) the making of a pathologic diagnosis of the localized lesion.

Endocrine dysfunction as caused by tumor of the brain in the parasellar region is considered.

A review of the pathogenesis, the typical symptomatology in childhood and the treatment of adamantinomas of the craniopharyngeal duct is offered.

The pediatric staff of the Indianapolis City Hospital cooperated in this study, and Dr. J. F. Kemp, Dr. E. Vernon Hahn and Dr. H. C. Thornton reviewed the manuscript and offered criticism.

Abstracts from Current Literature

Biochemistry; Bacteriology, and Pathology

A Study of the Biological Characteristics of Type III Pneumococcus Cultivated at Temperatures Below 37° C. Sophie Spicer, J. Bact. **39**:517 (May) 1940.

The author obtained a strain of the type III pneumococcus from the Rockefeller Institute. She then used various types of mediums in order to observe its growth in the laboratory. A fluid medium was employed. It consisted of beef heart phosphate broth of p_H 7.4 to 7.6. A solid medium was also tried for the pour and streak plates. It was made up of 2 per cent beef heart agar to which 3 per cent citrated horse blood was added. Finally (especially for "colony morphology") she made use of 5 per cent horse plasma instead of whole horse blood. With these mediums the growth of the organism was carefully observed, everything being kept constant except the temperature. Observations were made all the way from 37 C. down to 21 C. The optimum temperature for growth was found to be 27 C. However, the virulence of the organism for white mice did not change with variations in temperature. This study may be of value if there is any relation between the favorable growth at 27 C. and the production of type-specific serums. Further studies are in progress.

Stoesser, Minneapolis.

Variety of Types in Human Paratyphoid C Infections. F. Schiff and I. Saphra, J. Infect. Dis. **66**:97 (March-April) 1940.

Ten of nineteen known types of paratyphoid C bacillus have been found in the United States. Six types (Salmonella cholerae suis, Salmonella newport, Salmonella bareilly, Salmonella oranienburg, Salmonella montevideo, Salmonella muenchen) have been isolated from animals in this country; two other types (Salmonella bovis morbificans and Salmonella amersfoort), in animals in Europe or South Africa. Only two types, Salmonella virchow and Salmonella thompson, are not yet known as pathogenic in their action on animals.

Toomey, Cleveland.

Studies on Absorption Capacities of the Skin and Intestinal Mucosa. G. Kimura, Orient. J. Dis. Infants **27**:77 (March) 1940.

For the study of cutaneous absorption the author applied 5 Gm. of hydrous wool fat containing 15 per cent salicylic acid over an area 7 cm. square on the abdomens of albino rabbits. The quantitative estimation of the acid in body fluids revealed that the maximum absorption in the blood occurred in two to four hours after the inunction and was followed by a complete disappearance within seven to nine hours, whereas the maximal urinary excretion took place in three to five hours and a trace was detectable in the urine even after fifteen to twenty-four hours. The speed with which salicylic acid was excreted in the urine varied within thirty minutes in different animals; the total amounts of excretion fluctuated between 0 and 1.0 mg. (0 to 30 per cent). Moreover, the differences in time of the first appearance of the acid did not necessarily run parallel with those of the excretion. The rate of excretion was rapid in adult animals and relatively slow in young animals. There seemed to be a definite seasonable influence in the rate of urinary excretion, which was rapid during the summer and slow in the cold weather.

The rate of absorption from the mucous membrane of the intestine was measured by the quantitative estimation of salicylic acid in the blood and urine after its oral administration in doses of 0.1 Gm. per kilogram of body weight. The ingested acid first began to appear in the blood with the maximal concentra-

tion in five to seven hours, while the urinary excretion began in one-half to one hour, the maximum values being observed in seven to ten hours. When sodium salicylate was injected subcutaneously the highest blood concentration was found within one hour.

Under certain pathologic conditions the rates of absorption of the test substances were decidedly abnormal. In the presence of acute acidosis absorption from the skin was seriously hindered, as was evidenced by a low blood concentration and a diminished urinary excretion, whereas in the presence of alkalosis the opposite findings were obtained. Somewhat identical results, though less pronounced, were obtained in the rates of absorption from the intestinal mucosa under similar experimental conditions. In the presence of anaphylaxis the cutaneous absorption was remarkably increased during the incubation period and less so during the period of shock. The absorption from the intestinal mucosa followed a similar course, although less marked. When the reticuloendothelial system was blocked by intravenous injection of a sterile india ink suspension, both the absorption and excretion of salicylic acid given by mouth, smeared on the skin or injected subcutaneously were markedly delayed. In the animals with hepatic damage produced by intramuscular injection of chloroform in olive oil, a general decrease in the speed of both absorption and (consequently) excretion was observed.

KATO, Chicago.

Metabolism; Infant Feeding; Milk and Other Foods

DRY SKIM MILK IN LOW COST DIETS. ELEANOR P. HUNT, Child Development **10**:241 (Dec.) 1939.

This study was undertaken to appraise more fully the dietary and nutritional effects of the use of dry skimmed milk as a supplement in low cost diets deficient in milk products. The subjects studied were 213 preschool Negro boys living in the District of Columbia, whose estimated daily consumption of milk did not exceed approximately a cup of fluid milk or its equivalent in milk products. The subjects were divided on a geographic basis into a control group of 101 children and a demonstration group of 112 children. The families of the children of the demonstration group received throughout the period of the study regular supplements of dry skimmed milk. The nutritive value of the daily diets of the children of the demonstration group and of the control group was estimated by means of quantitative diet records, obtained for a sample of 11 experimental subjects and 6 control children. The milk supply of the 6 control subjects ranged from none to an amount equivalent to 360 Gm. of fluid skimmed milk per day. The median amount was equivalent to 90 Gm. of fluid skimmed milk. The median for the milk supply of the 11 demonstration subjects was equivalent to 820 Gm. of fluid skimmed milk. When the supplements of dry skimmed milk were sufficient to increase the consumption of milk of the demonstration subjects to the equivalent of 820 Gm. or more of fluid skimmed milk, the children of the demonstration group did not exhibit the evidences of dietary inadequacy with respect to good quality protein, energy value, vitamin B, riboflavin (vitamin G), calcium and phosphorus which were typical of those of the control group. Growth in stature during a period of approximately four months was more homogeneous and somewhat greater for the 4 year old demonstration group than for the corresponding series of the control group.

HUNT, Washington, D. C.

CYSTINE AND METHIONINE FOR GROWTH AND LACTATION. J. R. HAAG and L. D. WRIGHT, J. Nutrition **19**:563 (June) 1940.

Haag and Wright, in their experimental work with rats, noted that cystine and methionine are not unique as stimulants of lactation, serving primarily to make sulfur-deficient proteins adequate nutritionally.

FREDEEN, Kansas City, Mo.

IRRADIATED EVAPORATED MILK AS A FOOD FOR INFANTS: A STUDY OF GROWTH, ELIMINATION, PROTECTION FROM RICKETS, AND MORBIDITY IN UPPER RESPIRATORY INFECTIONS IN COMPARATIVE GROUPS FED ON IRRADIATED AND NONIRRADIATED EVAPORATED MILK. CLIFFORD G. GRULEE, HEYWORTH N. SANFORD and MATTHEW LEWISON, J. Pediat. **14**:725 (June) 1939.

In a study carried on for two years with a group of infants given irradiated evaporated milk and nonirradiated evaporated milk and viosterol in oil, the following facts were observed:

1. The average number of stools was practically the same for each group (2 per day for the group given irradiated milk and 2.3 per day for the group given nonirradiated milk).

2. In certain of the babies in both groups there was a tendency occasionally to have more than three stools per day. This tendency was noted oftener in younger infants. It was slightly more marked during the first weeks in the group given nonirradiated milk and during the later months in the group given irradiated milk.

3. The average gain per month was the same in both groups, 1.3 pounds (589.6 Gm.) per month.

4. None of the infants in the group given irradiated evaporated milk showed any signs of rickets either clinically or roentgenologically. Four infants in the group given nonirradiated evaporated milk and viosterol in oil showed slight signs of clinical rickets, but of these only 1 showed signs of rickets by roentgenogram.

FROM THE AUTHORS' SUMMARY.

EFFECT OF GELATIN ON POWER OF WOMEN TO PERFORM MAXIMAL ANAEROBIC WORK. F. A. HELLERBRANDT, ROZELL, RORK, and ELIZABETH BROGDON, Proc. Soc. Exper. Biol. & Med. **43**:629 (April) 1940.

Six healthy young women accustomed to severe physical activity performed exercise, maximal anaerobic in type and constant as to rate and speed, on an electrodynamic brake bicycle. Five of these worked at 290 watts subject output and 1 at 220. They rode to exhaustion, which was usually reached in less than sixty seconds. After a preliminary training period gelatin was added to the diets, and this was found to have no effect on the capacity of women to perform maximal anaerobic work and no apparent effect on improvement in power due to training.

HANSEN, Minneapolis.

SOY BEAN FLOUR WITH DRIED MILK. HELEN M. M. MACKAY, Arch. Dis. Childhood **15**:1 (March) 1940.

A mixture of equal parts of dried milk and soy bean flour, given to a group of infants, proved satisfactory as compared with dried milk fed to a control group.

The author thinks that it should be possible to market it at a price much lower than that of full cream dried milk, and it is suggested that owing to its relative cheapness it merits extended trial in countries where, for economic reasons, a satisfactory substitute for breast milk has hitherto been unobtainable.

KELLY, Milwaukee.

EFFECT OF PROLACTIN ON LACTATION IN NURSING WOMEN. MEAVE KENNY and EARL KING, Lancet **2**:828 (Oct. 14) 1939.

In the experiments described in this communication two preparations of prolactin, one from the pituitary gland of the ox and the other from that of the sheep, were administered to 43 women during lactation. The women were selected as deficient in milk secretion at different stages of this period up to the third month. In 3 cases secretion of milk was absent until administration of prolactin

was begun on the ninth or tenth day after delivery. All subjects were followed for at least three months, and most were seen during six or seven months. Forty-three women classified as having deficient lactation were observed as controls.

A total dose of 15 cc. (900 Riddle units) of prolactin was employed in each case, spread over five days. The substance was given intramuscularly.

The response was encouraging, and the quality of the milk secreted was essentially the same as that of the samples taken from the controls.

LANGMANN, New York.

DIET AND OSTEODYSTROPHIC DISEASES IN DOMESTIC ANIMALS. A. I. MALAN, South African M. J. **14**:261 (July 13) 1940.

Bone atrophy and its acute form, osteoporosis, result primarily from increased bone resorption, which invariably takes place in animals receiving a diet deficient in one or more of the necessary nutrients, organic as well as inorganic. Bone atrophy and osteoporosis were produced in pigs fed on a ration adequate in all respects except protein. Rickets in animals is a phosphorus deficiency disease and is merely intensified by such contributory factors as excess calcium or absence of vitamin D. True rickets has never been shown to occur in animals receiving a diet low only in calcium. It is suggested that rickets in infants is always preceded by a period of food shortage or dietetic disturbance, such as takes place during sickness. The classic example of a bone disease from a dietary deficiency of calcium is bran disease, or bighead (osteodystrophia fibrosa) in horses. Rations low in calcium were fed to horses, cattle, sheep, goats and pigs, and in all but the pigs osteodystrophia fibrosa was produced, accompanied by osseous atrophy and osteoporosis but not by rickets. The author concludes that rickets, or osteomalacia, and osteodystrophia fibrosa are two etiologically distinct diseases, the former being the result of phosphate insufficiency and the latter of a deficiency of calcium in the diet of animals.

GONCE, Madison, Wis.

THE WATER-SALT EXCHANGES IN THE COURSE OF DEHYDRATION IN INFANTS. LUCIEN GAROT, O. GULKO and C. GOTTSCHALK, Rev. franç. de pédiat. **14**:588, 1938.

The authors studied the effects of a demineralized diet prepared from washed casein (30 Gm.), sugar (50 Gm.), dextrin (80 Gm.), butter (15 Gm.) and water to make 1 liter, on a series of infants. They then studied the effects of the same diet with addition of sodium chloride. Four children were studied for the effect on weight. The loss in weight as well as the gain when salt was added showed considerable variations. The authors conclude that the organism is able to maintain its weight equilibrium in the absence of mineral salts for several days (four to six in the experiments). In the next 2 cases urinary sodium, chloride and potassium were studied. It is apparent that with the demineralized diet the body begins to conserve all three elements. In a third case, instead of potassium the excretion of urea was studied and was found to be increased. A relative diuresis developed in all 3 cases, and the loss of water greatly exceeded the loss of sodium and chloride.

A case of spontaneous dehydration was also studied. The child had been poorly cared for and at the age of 1 year weighed only 5,800 Gm. The urinary output was small, most of the water loss probably occurring through the skin and the lungs. The urinary sodium, chloride and potassium concentrations were also very low. With the administration of sodium chloride a rapid gain in weight occurred, and there was at first a remarkable retention of sodium and chloride, with the development of fever until abundant water was supplied. After this the urinary sodium, chloride and potassium increased; the amount of urine doubled, and the perspiration diminished.

LESLIE, Evanston.

Hygiene; Growth and Nutrition; Public Health

MATERNAL DEATH RATE IN THE ARGENTINE REPUBLIC. CARLOS ROUST, Bol. Inst. internac. am. de protec. a la infancia **13**:544 (Jan.) 1940.

The author establishes that the index of maternal death rate is in direct relation to the obstetric assistance, the social aid given to the mother and the cultural and hygienic level of each region. The index of maternal mortality is the coefficient of the relation between the deaths due to diseases or accidents of pregnancy, childbirth or the puerperal state and every thousand born alive during a certain time, generally one year. The index in the Argentine Republic was as follows: 1911, 4.5; 1920, 3.76, and 1935, 3.56. This demonstrates that the death rate is decreasing.

FROM EDITOR'S SUMMARY.

A PANAMERICAN EDUCATIONAL IDEAL. ARTURO PIGA, Bol. Inst. internac. am. de protec. a la infancia **13**:812 (April) 1940.

The author studies the characteristics of an ideal for youth and asks whether there is at present an American ideal already in action or about to be so; after studying the different features of the matter he asks whether anything has been done for the American youth—anything of a political, social, economic or simply cultural kind, susceptible of being an ideal that might unite all the races of the American continents.

In the Latin American countries the answer is in the affirmative; Latin Americans understand one another, love and help one another with a spiritual generosity devoid of distrust and without limitation or hope of reward. Nevertheless, the author had in mind the hybrid problem and the danger of foreign capital, danger hidden, as a Chilean writer says, in "the organization, spirit of enterprise, the highest culture and the abundant national richness of the countries that wish to conquer the markets and change them into factories, or to buy one by one the sources of riches, acting thus as the most gloomy prospect and categorical threat for the Hispanic continent."

FROM THE EDITOR'S SUMMARY.

"PAIDOPHYLAXIS," OR PRESERVATION OF CHILDHOOD. LUIS FELIPE GONZALEZ, Bol. Inst. internac. am. de protec. a la infancia **14**:73 (July) 1940.

It is suggested to introduce into the scientific lexicon the term "paidophylaxis," the etymologic origin of which indicates preservation of the child. The aim should be to preserve infancy from the evils that afflict it, to study and apply scientific principles to assure the gestation and birth under the best conditions and to supervise the child's whole development up to the moment in which he is able to fend for himself and to be an active element in society.

FROM AUTHOR'S SUMMARY.

PROBLEMS AND TASKS OF PEDIATRICS IN TURKEY. A. ECKSTEIN, Ann. pædiat. **155**:16 (April); 57 (May); 113 (June) 1940.

The tasks and problems of pediatrics in Turkey differ in many respects from those in western Europe. These differences are influenced by the peculiarities of the climate, of the social factors and of the age structure of the population. Over 87 per cent of all the children in Turkey live in the rural districts. The proportion of children to the total population has a broad base, while there are differences between the rural and the urban population. My own investigations, carried out in the interior of twenty-five provinces of central and western Anatolia, supplement the existing statistics and give a clear idea of the birth rate and also of the death rate among infants up to 1 year and among older children. Births were found to be increasing regularly, and the average number of living children per woman between 40 and 44 years of age is 3.71. The number of births ranges from an average of two for women between 18 and 24 up to six and

twenty-one hundredths for women of 45 and over. The investigations concerned 23,628 women in 188 villages. With the younger mothers the infantile mortality remains within moderate limits; it is higher with the older ones, but, as women in the rural areas marry at an early age, many deaths among the so-called children occur at an adult age. This is also the reason why former estimates of mortality among children in rural areas were too high. Infantile mortality is about 20 per cent in the rural districts but is probably lower in towns.

The laws for child protection and the development of pediatrics in Turkey are stated and the peculiarities considered.

The problem of the rearing of the suckling is distinguished fundamentally from that in western Europe by the fact that about 90 to 95 per cent of all the infants are breast fed for at least twelve months. There is no hourly plan for feeding; the infant is put to the breast instinctively, not infrequently ten or twelve times during twenty-four hours. The children thrive very well in this way, and the mothers also feel well with this technic, especially as the productiveness of the breast is evidently thereby enhanced.

The most important diseases of infancy are discussed. The chief cause of vomiting is a faulty technic of suckling (no wind allowed to be brought up). Pyloric stenosis was observed only twice, in foreigners. Diseases due to stone are frequent in infants as well as in older children. As this fact cannot be attributed to the diet (which in most cases consists only of breast milk), constitutional factors must be inferred. The exudative diathesis comes only rarely under observation and is said to occur more frequently in the districts around the Black Sea. Spasmophilia has been rarely observed and then in breast-fed infants. Rickets is also rare in the district of Ankara and occurs mostly in artificially fed children. It is to be stressed, however, that climatic factors (strong sun rays even in the winter at an altitude of about 3,000 feet) act as an antirachitic. Rickets in breast-fed children has been observed in several Anatolian provinces with a poor population, the condition occurring frequently and to a severe degree.

Diarrheic illnesses are the great pediatric problem in Turkey. Generally they have an infectious origin. They are not due to direct damage by heat, especially as the epidemic decreases at the acme of the heat wave. In a considerable number of cases the author observed infantile typhoid, but it seems that the most important organism is the "dyspepsia-coli." Serum treatment with a polyvalent antidysentery serum, the effect of which could not be considered specific, has given excellent results. Experiments with prophylaxis and treatment with bacteriophages are in progress.

During the hot season thirst fever occurs not infrequently in children fed incorrectly diluted dried milk. The peculiarities of infectious diseases of children in Turkey are discussed in general and especially typical examples are given. Among 205 infants treated in the hospital for bronchopneumonia the death rate was high (53.6 per cent). In contrast to conditions in western Europe, this high mortality persists up to the sixth year, which is responsible for the fact that the death rate of a total of 411 children up to 12 years of age was 50.6 per cent. More than half the deaths occurred during the first forty-eight hours after admission. Tests at random for the types of pneumococci resulted in finding a preponderance of type X.

Among 237 children with lobar pneumonia the author found 11 in their first year, which corresponds with Engel's experiences. The mortality among children with lobar pneumonia was also fairly high (15.6 per cent). However, one fifth of all the deaths occurred during the first forty-eight hours after admission. Tests at random for the types of pneumococci showed a greater proportion of type X than was found among adults in Ankara.

Malaria is prevalent in some districts. The differences between the signs and symptoms of malaria in childhood and in adulthood are generally not sufficiently stressed. This applies particularly to malaria in infancy (no rigor, intes-

tinal form with diarrhea, malarial bronchitis). The mortality from malaria among infants in their first year in the malarial districts seems to be less than that of children in later infancy. Already in the second year of life there are children with chronic malaria, which, apart from the typical manifestations (cirrhosis of the spleen and liver), leads to severe dystrophy. The author has published observations on older children with malaria and simultaneously occurring hemorrhagic nephritis and also those on coma and blackwater fever. He has also described a few observations concerning the propagation of malaria *e medico* (blood transfusions, blood injections). He had to confirm the heretofore rare observation of the spread of malaria through intramuscular injections of blood. His experience in the treatment of chronic malaria with intravenous injections of epinephrine according to Ascoli's method and the activation of the illness produced has induced him to discard this method.

On the other hand, he has come to the conclusion that atabrine, particularly in combination with plasmochin, gives very good results in children with acute and chronic forms of this disease about which so far little is known.

His experiences with the course of typhoid are based on 185 patients treated in the hospital. The percentage of younger children with this disease is considerably higher than in western Europe; e. g., in children in the first year of life it is 10.3 per cent as compared with 0.6 per cent of the Prague material; in children from 1 to 4 years old it is 18.4 per cent as against 7 per cent. The peculiarities of infantile typhoid are pointed out. Leukopenia was a valuable symptom according to his experiences. The course of typhoid is neither more nor less favorable than in western Europe.

Noma occurs fairly frequently in certain districts of Turkey. His first experiences gained from 40 cases treated in the hospital have already been published (Am. J. Dis. Child. **59**:219, 1940).

The author's experiences in the treatment of diphtheria differ little from his observations in western Ge.many. He has generally given higher doses of serum, because he has observed that here the membranes take longer to separate. The proportion of severe ailments in his clinical material (toxic diphtheria and stenosis) was fairly high, because he treated all milder conditions in the outpatient department.

Eckstein's observations on epidemic meningitis were interesting so far as he found that, among 50 patients, school children were preponderant, whereas in western Europe chiefly infants are affected. The author obtained remarkable results with serum. If the 6 patients who died within the first forty-eight hours after admission are deducted, 40 of 44 patients up to 14 years of age were cured. The author believes that these good results were due to the fact that the serum is manufactured from local strains in the state serum works in Ankara.

In connection with this the author reports his experiences with serum rashes. Of 400 children treated with horse serum (antidiphtheritic and others) the percentage of those affected was relatively small. So far Eckstein has not been able to determine whether this was caused by special peculiarities of the serum prepared in Ankara or was due to certain constitutional factors in his patients.

Further investigations were made concerning the frequency of tuberculosis by using cutaneous tests. Researches included studies of children from Ankara (hospital and outpatient department) as well as of children from the villages of central Anatolia. Eckstein compared his results with the investigations made by Hüametin Kural among village children and by Kadri Rajid in Istanbul. He found that the number of positive reactors in rural areas as well as that in Ankara was fairly low, but in Ankara it was higher than in the rural areas. The number of positively reacting children in Istanbul was considerably higher. This also corresponds to the number of registered deaths from tuberculosis in Ankara and Istanbul. The type and frequency of extrapulmonary tuberculosis in rural areas are pointed out.

From the Author's Summary.

Newborn

FACTORS INFLUENCING PLASMA PROTHROMBIN IN THE NEWBORN INFANT: III. A STUDY OF THE VITAMIN K ACTIVITY OF VARIOUS NAPHTHOHYDROQUINONE DERIVATIVES. L. M. HELLMAN, WILLIAM T. MOORE and LANDRUM B. SHETTLES, Bull. Johns Hopkins Hosp. **66**:379 (June) 1940.

In small, unit-equivalent doses, 2-methyl-1, 4-naphthoquinone, 2-methyl-1, 4-naphthohydroquinone dipropionate and 2-methyl-3-phytyl-1, 4-naphthoquinone dissolved in oil are capable of raising the level of plasma prothrombin in the newborn infant when given by mouth to the mother during labor.

In similar doses, intravenous 2-methyl-1, 4-naphthohydroquinone-3-sodium sulfonate is shown to possess significant vitamin K activity.

On the contrary, under identical conditions, 2-methyl-1, 4-naphthoquinone in milk sugar pills, and vitamin K concentrate, given by mouth, and 2-methyl-1, 4-naphthohydroquinone-3-sodium sulfonate, given intramuscularly, could not be shown to be effective in raising the plasma prothrombin levels of the newborn infants.

AUTHORS' SUMMARY.

RESUSCITATION OF THE NEWBORN. ROBERT J. KESSLER, Pennsylvania M. J. **43**:1411 (July) 1940.

The author feels that asphyxia in a large number of cases may possibly be prevented by a careful selection and dosage for analgesia and anesthesia and that mild asphyxia responds to gentle handling, clearing of the airway and application of external warmth. In cases of severe asphyxia direct laryngoscopy with removal of debris and mucus from the trachea and the introduction of oxygen directly into the trachea is the method of choice. If a stimulant is necessary, lobeline injected into the umbilical vein is probably the most satisfactory.

LOGUE, Williamsport, Pa.

EFFECT OF RELATIVE HUMIDITY ON SKIN AND RECTAL TEMPERATURES OF THE NEWBORN INFANT. JOHN A. ANDERSON, Proc. Soc. Exper. Biol. & Med. **44**:466 (June) 1940.

In an attempt to explain the physiologic processes involved in the decrease in insensible loss of weight of the unclothed newborn boy, the temperatures of the cutaneous surface and of the rectum were taken at low and high environmental relative humidity. Associated with a decrease of 1.63 Gm. of insensible loss of weight per hour, there were a definite increase in the surface temperatures of the foot and the hand and a slight increase in the surface temperature of the abdomen and the forehead. The increase in the surface temperature of the body of the newborn infant induced by increasing the relative humidity of the environmental air offers an explanation of the mechanism involved in the decrease of the insensible loss of weight under the same conditions. These responses are similar to those reported for adult subjects under the same conditions.

HANSEN, Minneapolis.

EFFECT OF DEPRIVING NEWBORN OF PLACENTAL BLOOD UPON EARLY POSTNATAL BLOOD PICTURE. Q. B. DEMARSH, W. F. WINDLE and H. L. ALT, Proc. Soc. Exper. Biol. & Med. **44**:662 (June) 1940.

The value for hemoglobin and the red blood cell count were determined for 25 babies on whom the umbilical cord was clamped within thirty seconds after birth and for 29 babies for whom clamping was delayed until after pulsations had ceased and the placenta had separated. The umbilical cord blood contained 15.7 Gm. of hemoglobin per hundred cubic centimeters. Within a short time (less than an hour in these experiments) the value for hemoglobin rose to 21.3 Gm. per

hundred cubic centimeters and the red blood cell count to 5,930,000 per cubic millimeter for those infants who were allowed to retrieve their placental blood; for those infants with the cord cut within thirty seconds the value for hemoglobin rose to only 18.9 Gm. and the erythrocyte count to 5,570,000. The reticulocyte counts for the infants with the cord cut immediately were higher. The authors believe that a drain is placed on the child's iron reserve if the cord is cut early.

HANSEN, Minneapolis.

ERB-DUCHENNE PARALYSIS IN THE NEWBORN. ARGELIO GARCÍA LÓPEZ, Arch. de med. inf., Habana **9**:176 (July-Sept.) 1940.

A case is reported. Statistics show that the frequency is 1 in 2,000 births. The differential diagnosis rests between separation of the scapulohumeral joint and the pseudoparalysis of Parrot. The child improved with rest alone. This is the first treatment; the second is electrical stimulation, and the third is operation.

SANFORD, Chicago.

FETAL ERYTHROBLASTOSIS IN ONLY ONE OF UNIOVULAR TWINS. ISRAEL MAHARIK, Ann. pædiat. **155**:107 (May) 1940.

Erythroblastosis with generalized dropsy is reported as occurring in only 1 of uniovular twins whose mother suffered from primary hypochromic anemia. The conclusion is drawn that erythroblastosis should not be reckoned among the hereditary diseases but that it appears phenotypically if during pregnancy a further injury—in this case perhaps the mother's anemia—hampers the development of the placental part of the fetal hematopoietic organs.

FROM THE AUTHOR'S SUMMARY.

THE KOFFERATH SYNDROME. L. MEŁAMED, Acta pædiat. **27**:79, 1939.

This is the report of a case of obstetric injury to the brachial plexus and the phrenic nerve, leading to paralysis of an arm and half of the diaphragm. The statement is made that the syndrome was first described by Kofferath. To the reviewer's undisguised surprise it is characterized as a rare complication of delivery. Prognosis, prevention and treatment are discussed briefly. The bibliography is useful.

MCCUNE, New York.

THE PROTHROMBIN CONTENT IN RELATION TO EARLY AND LATE FEEDINGS OF THE NEWBORN: A PRELIMINARY REPORT. L. SALOMONSEN and K. NYGAARD, Acta pædiat. **27**:209, 1939.

Almquist and his co-workers have demonstrated that an antihemorrhagic factor similar to or identical with vitamin K is produced by the metabolic activity of certain bacteria. To test the significance of this fact in relation to hemorrhagic disease of the newborn, Salomonsen carried out measurements of the prothrombin time and in some cases of the clotting time in two series of newborn infants who received different amounts of food within the first twenty-four hours of extrauterine life. All were breast fed: The 12 infants in the first group did not nurse for the first time until they were from 12 to 20 hours old; the 13 members of the second group were given supplement of diluted boiled cow's milk from two hours post partum up to the time when breast feeding was started. Serial observations during the first week of life revealed significant elevation of the prothrombin time and prolongation of the clotting time in the blood of the infants who received no supplement. Greater prolongation was encountered in 3 infants who were unintentionally starved for a longer period. In view of the fact that milk contains little preformed vitamin K, the phenomenon is probably due to bacterial activity.

The relation between the finding and hemorrhagic disease is discussed. Sanford is cited to the effect that hemorrhagic disease of the newborn does not occur if supplemental feeding of diluted cow's milk is instituted four hours after delivery.

McCUNE, New York.

A CASE OF BENIGN IDIOPATHIC ANEMIA NEONATORUM. A. L. AMLIE, Acta pædiat. **27**:273, 1939.

Although for a time there was a disposition to regard all primary, idiopathic anemia in the neonatal period as related to icterus gravis, it is now becoming apparent that there is a benign type that probably constitutes an independent entity. According to Lehndorff, this benign neonatal anemia is characterized by (*a*) lack of obvious cause, (*b*) sudden appearance, (*c*) paucity of symptoms and (*d*) a tendency to spontaneous and permanent cure. The case report concerns an 18 day old girl who was noted to become suddenly pale when she was 2 weeks old. The value for hemoglobin fell to 30 per cent without the development of symptoms or the appearance of pathologic physical signs of any sort. Treatment for ten days with an iron preparation was followed by a sudden rise of the hemoglobin concentration to 80 per cent. The infant continued to gain weight during the episode.

McCUNE, New York.

STUDIES OF THE PROGNOSIS FOR INFANTS BORN BY CESAREAN SECTION. O. BRANDBERG, Acta pædiat. **27**:403, 1940.

The fate of 367 infants born by cesarean section is traced; in 292 cases the classic operation was performed, and in 76 the vaginal route was taken. The two sexes were equally represented in the series and showed no difference with respect to mortality. Eight per cent of the infants born by vaginal section were found dead at birth or died within two hours. Their cases are excluded from further consideration, since their demise can be reasonably attributed to the desperate circumstances that led to the choice of operative delivery. With this allowance, the mortality during the first month of life was 4.8 per cent for the infants born by classic section and 23.5 per cent for those born by vaginal section. The former figure compares favorably with the prevailing death rate for newborn infants. Without allowance or correction, the death rate among premature infants was 66.7 per cent, and for full term infants, 9.9 per cent. These figures possess considerable significance, since 78 members of the group were born prematurely. The indication for operation played an important role: Elective section undertaken to procure a living child was attended by a negligible mortality; operation resorted to in emergency for the purpose of saving the life of the mother was responsible for most of the deaths. With respect to loss of weight during the first week of life, the infants born by section did no worse than infants born naturally; however, they regained their birth weight somewhat more slowly. Apnea and asphyxia were not unduly prominent.

Of the 288 infants who survived, follow-up information concerning 234 was obtained by questionnaire or medical examination after varying intervals. Five per cent of the children were found to be mentally defective or to suffer from various neurologic disorders. In only about half of the cases did reasons other than birth trauma account for the disability. An incidence of about 2 per cent is calculated for intracranial injuries clearly ascribable to classic section and of 13 per cent to vaginal section. The suspicion is expressed that these estimates would be higher had more autopsy material been available. The source of the references in the ample bibliography suggests that the topic has aroused greater interest abroad than in the United States.

McCUNE, New York.

Acute Contagious Diseases

FULMINATING MENINGOCOCCAL SEPTICEMIA WITH BILATERAL SUPRARENAL HEMORRHAGE. EMMA S. MOSS and JOHN R. SCHENKEN, New Orleans M. & S. J. **93**:294 (Dec.) 1940.

The authors report 2 cases of fulminating meningococcic septicemia with bilateral hemorrhage of the adrenal glands. As in 70 per cent of the cases of this disease, the patients were both under 2 years of age (18 months).

The initial symptoms in the cases reported were convulsions in one and dyspnea in the other. The usual symptoms are a sharp cry followed by alternating cyanosis and pallor. Purpura appeared in each case within a few hours after the onset. Organisms were found in the blood smears in the second case, and a search for them in any suspected case is recommended as a method of making an early and accurate diagnosis.

Clinical signs of meningitis were absent in each case, although autopsies proved the presence of meningeal involvement. In both cases the characteristic hemorrhages in the adrenal glands were present.

BERKLEY, Los Angeles.

PREVALENCE OF COMMUNICABLE DISEASES IN THE UNITED STATES. Pub. Health Rep. **55**:2143 (Nov. 22) 1940.

For the period of Oct. 6 to Nov. 2, 1940, influenza, measles and poliomyelitis were above the median prevalence. Influenza, with 3,300 cases, was 10 per cent above; measles, with 6,083, was 35 per cent above, and poliomyelitis, with 2,859, was almost twice the median figure. All other diseases were below the median. The average mortality from all causes was 11 per thousand of population.

SANFORD, Chicago.

THE RELATIVE ERROR IN EXAMINING SWABS FOR CORYNEBACTERIUM DIPHTHERIAE BY THE LOEFFLER SLOPE AND BY THE CLAUBERG PLATE. H. WILSON, M. J. Australia **2**:373 (Oct. 19) 1940.

An analysis of 180 errors in 1,115 swabs showed: (*a*) that the error of commission (reporting of a swab as "positive" when Corynebacterium diphtheriae was not present) with the Loeffler method was 14.7 per cent and with the Clauberg method 7.5 per cent; (*b*) that the error of omission (reporting of a swab as "negative" when C. diphtheriae was present) with the Loeffler method was 15.4 per cent and with the Clauberg method was 1.8 per cent.

GONCE, Madison, Wis.

PREVENTION OF PULMONARY COMPLICATIONS IN DIPHTHERIA. A. LUBRANO and V. LANZA, Pediatria **47**:878 (Oct.) 1939.

The authors discuss the frequency and severity of the pulmonary complications of diphtheria. They attempted to prevent these complications by giving one group of children suffering from diphtheria a prophylactic injection of an antipneumococcus vaccine on admission to the hospital. Another group was given 20 cc. of a polyvalent pneumococcus serum, and another was given a combination of the serum and the vaccine. The authors claim a reduction in the number of complications and a lowering of the mortality.

MARTOCCIO, Utica, N. Y.

BLOOD NITROGEN AND CHLORIDES IN DIPHTHERIA. E. CECCHI and V. LANZA, Pediatria **47**:962 (Nov.) 1939.

The authors determined the values for nitrogen and chlorides in the blood of 52 patients with diphtheria. They found that the concentration of nitrogen was almost always elevated but that the increase was not related to the severity of the disease. It is impossible to formulate a prognosis from such values. The

values for blood chlorides were frequently decreased. In cases of severe diphtheria the uric acid concentration was increased. There was no change in the creatinine content.

MARTOCCIO, Utica, N. Y.

INVESTIGATIONS OF THE TOXICITY OF CERTAIN ORGANS IN EXPERIMENTAL DIPHTHERIAL INTOXICATION. F. SEMAH, Acta pædiat. **27**:219, 1939.

In support of the concept that diphtheria toxin has some of the properties of an enzyme, the author reports successful experiments in which it was found possible to kill healthy guinea pigs with extracts of the organs obtained from other guinea pigs which had been inoculated with fatal doses of diphtheria toxin. Extracts of the organs of the second animal killed a third, those from the third a fourth and those from the fourth a fifth. As the toxin originally injected must necessarily have been diluted by the repeated transfers to a point far below a lethal dose, the experiments suggest the presence in diphtheria toxin of an enzyme that affects the body cells so as to produce an additional noxious substance, a so-called histotoxin.

McCUNE, New York,

POLIOMYELITIS AND THE METEOROLOGICAL ENVIRONMENT. W. F. PETERSEN and A. MAYNE, Acta pædiat. **27**:353, 1940.

An examination of the correlation between the state of the weather and the incidence of poliomyelitis in several individual instances, as well as in the Chicago epidemic of 1916 and the New York epidemic of 1931, leads to the conclusion that the meteorologic situation plays an important role in conditioning individual susceptibility to the disease. Both the prodromal symptoms and the advent of paralysis show a disposition to be initiated by the passage of a mass of cold air over the community. Physiologic considerations are adduced to rationalize the findings, and Hippocrates is quoted to lessen its novelty.

McCUNE, New York,

A CASE OF POSTVACCINAL ENCEPHALITIS IN A CHILD WHO HAD PREVIOUSLY BEEN AFFLICTED WITH MYASTHENIA GRAVIS PSEUDOPARALYTICA. L. GRÖNLUND, Acta pædiat. **27**:495, 1940.

A 2 year old girl suffered an illness characterized by symptoms of the classic myasthenia syndrome. Some improvement appeared after three months of care in the hospital; at the end of two years more she was vaccinated against smallpox by the multiple scratch method. Ten days later an acute encephalopathy made its appearance; after a four day illness she died. The diagnosis of encephalitis was confirmed at autopsy. Efforts to transmit the disease to animals by inoculating them with ground fragments of the basal ganglions were fruitless.

Since the occurrence of myasthenia gravis and postvaccinal encephalitis in one and the same child is apparently unique, it is necessary to assume some causal relation between the two diseases in this case. A somewhat nebulous hypothesis is elaborated and discussed.

McCUNE, New York,

Acute Infectious Diseases

A NINTH YEAR'S OBSERVATIONS ON MALARIA IN PANAMA, WITH REFERENCE TO THE OCCURRENCE OF AN EPIDEMIC FOLLOWING CONTINUED TREATMENT WITH ATABRINE AND PLASMOCHIN. H. C. CLARK, W. H. W. KOMP and D. M. JOBBINS, Am. J. Trop. Med. **20**:47 (Jan.) 1940.

The population studied had been under observation and treatment with various drugs since 1931. No correlation between the annual rainfall and the monthly rates for malarial parasites was shown. The parasite rate, cumulative for twelve months, showed a small increase in the number of persons with parasites in the

blood. The incidence of the various species of parasites was nearly the same as in previous years. The parasite rate among 65 infants less than 1 year of age was 1.5 per cent.

In spite of continuous treatment with three potent drugs an epidemic occurred during the last few months of the period of observation. For the first time since this study began data were obtained on the relation of mosquito density to rates of malaria.

BURPEE, Augusta, Ga.

FOOD-BORNE INFECTION WITH SALMONELLA AERTRYCKE. EARLE G. BROWN, G. R. COMBS and EVAN WRIGHT, J. Am. M. A. **114**:642 (Feb. 24) 1940.

An outbreak of Salmonella aertrycke infection occurred in an orphanage and involved 55 boys and 16 adults, with 1 death. The authors describe the progress of the knowledge of so-called food poisoning and the reported incidence of such conditions. The method of tracing the source of this epidemic is described. All the patients had eaten a pudding which had as an ingredient duck eggs from ducks which were shown to have positive Salmonella infection in the oviducts in 2 instances. Their infection probably was of human fecal origin, and Salmonella aertrycke was grown from stools of the farmer, the ducks and 17 of the involved patients.

HEERSMA, Kalamazoo, Mich.

SPLENECTOMY AND BENZOL INJECTION AS MEANS OF INCREASING SUSCEPTIBILITY OF CHINESE HAMSTERS TO KALA-AZAR. C. W. WANG and HUI-LAN CHUNG, Proc. Soc. Exper. Biol. & Med. **44**:35 (May) 1940.

In a study using 60 Chinese hamsters (Cricetulus griseus), splenectomy was performed on 20; benzene was injected into 20, and the remaining animals were used as controls. Then Leishmania donovani (0.2 cc. of the culture, estimated to contain 145,000 flagellates) was injected intraperitoneally. Both splenectomy and injection of benzene, especially the former, rendered the experimental animals more susceptible to kala-azar infection.

HANSEN, Minneapolis.

SOME ASPECTS OF STREPTOCOCCIC INFECTION: A REVIEW. T. J. MACKIE, Edinburgh M. J. **47**:466 (July) 1940.

This communication from the department of bacteriology of Edinburgh University presents a good review of the present state of knowledge. The author believes that a marked impetus was given to the study of the streptococci by the work of George and Gladys Dick in 1923. Since then there has been a steady increase in what is known about these organisms, and most recently the accomplishments of chemotherapy as applied to streptococci have opened a new chapter in the treatment of many other bacterial infections.

Systems of classification of groups and hundreds of strains do not reveal any essential difference among the hemolytic types which cause scarlatina, erysipelas, puerperal sepsis, acute tonsillitis and suppurative lesions. For example, of 2 persons infected with the same strain (neither person having ever had clinical scarlet fever) 1 may present the scarlatinal syndrome; the other may have only a sore throat, because there may have been previous streptococcic infections from which he has acquired sufficient antitoxin to prevent effects of the erythrogenic toxin. Strains from other conditions, such as erysipelas, puerperal sepsis and surgical scarlet fever, may be erythrogenic.

In many cases of scarlet fever observed in hospitals it has been found that suppurative complications, such as otitis and adenitis, are due to a new infection by a different type of hemolytic streptococcus through a cross infection from patient to patient. The author cites de Waal as having found these organisms in the air of wards and cubicles where various types of infection may be present. Bacteria are diffusible in the air of a ward, and certain ones may spread even a distance of 41 yards (37 meters) within a few minutes.

The author closes with a discussion of the prevention of streptococcic infection. Some of the problems mentioned belong to public health administration. A second line of defense is needed in promoting increased resistance to these organisms, though it is a fact that natural immunization is going on because of contact with these prevalent infections. The third line of defense is the use of sulfanilamide and its derivatives, which is already controlling certain forms of streptococcic infection which would otherwise prove serious or fatal.

NEFF, Kansas City, Mo.

BACTERIOLOGY OF RHEUMATIC FEVER. W. R. F. COLLIS, Lancet **2**:817 (Oct. 14) 1939.

In seventeen autopsies on patients who died of rheumatic fever, hemolytic streptococci were grown from the centers of fourteen of fifteen tonsils, from thirteen of twenty-seven cervical or mediastinal glands and from twenty-two of forty-two heart valves.

From twelve valves in cases in which the blood of the heart was sterile a pure growth of hemolytic streptococci was obtained. From five valves in cases in which the blood of the heart contained Streptococcus viridans at death, both hemolytic streptococci and Str. viridans were cultured. From five valves in cases in which the blood of the heart was sterile hemolytic streptococci and some other organism were obtained. From four valves (three from one heart) in cases in which the blood of the heart was sterile, Str. viridans or gamma streptococci were grown.

The recent findings of Green, namely, the culture of hemolytic streptococci from the heart valves of 8 of 9 patients who died in an acute or subacute phase of rheumatic fever, prompted Collis to publish his findings.

LANGMANN, New York.

ANTISTREPTOLYSIN S TITRES IN RHEUMATIC FEVER. E. W. TODD, ALVIN F. COBURN and A. BRADFORD HILL, Lancet **2**:1213 (Dec. 9) 1939.

An investigation has been made of the antistreptolysin S and antistreptolysin O titers in the serums of (1) normal adults; (2) nonrheumatic children with or recovering from hemolytic streptococcic infections; (3) rheumatic children suffering from similar infections but with no rheumatic activtiy, and (4) rheumatic children in whom the streptococcic infection was followed by an acute attack of rheumatic fever.

Although, naturally, there is much variability from one person to another, the general trend of the figures leads to the following conclusions: 1. In response to infection with the hemolytic streptococcus there is a rise in the antistreptolysin S titer considerably above the normal level in the serums of nonrheumatic children and in the serums of rheumatic children without signs of rheumatic activity. 2. In the serums of children with clinical signs of rheumatic activity the antistreptolysin S titer, although often above normal, tends to remain relatively low. 3. Serums taken during the period of acute rheumatic fever show lower antistreptolysin S titers than serums taken from the same patients during periods of rheumatic inactivity. During rheumatic attacks the titer varies with the intensity of the rheumatic process, tending to be lowest when the clinical symptoms are most pronounced. 4. The antistreptolysin O titers tend to be higher in rheumatic subjects who contracted pharyngitis but escaped rheumatic attack than in nonrheumatic children with pharyngitis or scarlet fever. A more pronounced increase is shown by children with active rheumatic fever, and the titer tends to be highest at the height of their attack or just subsequently. 5. There is a striking contrast between the low antistreptolysin S titers and the high antistreptolysin O titers associated with rheumatic fever.

FROM AUTHORS' SUMMARY.

BANG'S DISEASE IN A PREMATURE INFANT. EMMY BUSER-PLÜSS, Schweiz. med. Wchnschr. **10**:208 (March 9) 1940.

The author describes the infection of a premature infant with what was doubtless Bacillus abortus Bang. There was the typical syndrome of undulant fever, with numerous complications in the respiratory organs—catarrh, otitis and bronchopneumonia. After several months the child recovered.

Although it cannot be said definitely that an intrauterine infection caused the disease, the following factors point to this causation: (1) latent infection of the mother with Br. abortus during or shortly before pregnancy; (2) premature birth at 6 months, presumably as a result of the infection of Bang's bacillus; (3) the insidious onset and slow progression of the undulant fever in the child during the first months of life—an age when there is immunity to an exogenous infection with Br. abortus.

ABT, Chicago.

MALARIA IN WESTERN YUNNAN, WITH REFERENCE TO THE CHINA-BURMA HIGHWAY. R. CECIL ROBERTSON, Chinese M. J. **57**:57 (Jan.) 1940.

Malaria is present to the same extent on both sides of the China-Burma line. Malaria has caused innumerable deaths during the construction of the new motor highway from Kunming to Lashio, in the Northern Shan State.

The author reports the incidence among the general population. Information is difficult to obtain, because the hereditary chieftain is not greatly concerned with hygienic measures for the people, who believe that a person should take herbs. Several attacks occur usually before the sick person is given quinine.

In the district of Chafeng, a survey of school children for June and July showed a splenic index of 30 and an index of 75 per cent for parasites, all of the subtertian variety. In Hsitsa, plasmodia were found in 90 per cent, and in Monka, in 93 per cent. Usually the children show few definite symptoms. Shan children in Mangshih are infected with the ring forms of the subtertian parasite. Transport workers, such as coolies, have 80 per cent of infection. Response to treatment with five days' administration of a daily dose of 15 grains (0.97 Gm.) of quinine has been good, there having been only 2 deaths in 600 cases in Mangshih.

Fourteen species of Anopheles were recognized in the region where the survey was made. The author mentions antimosquito measures and the dependence which must be placed on prophylaxis by means of quinine for the immigrant population.

NEFF, Kansas City, Mo.

Chronic Infectious Diseases

THE PHYSICIANS IN TUBERCULOSIS CASE-FINDING. EZRA BRIDGE and ARELYN THURSTON, Am. Rev. Tuberc. **41**:444 (April) 1940.

Of 1,000 patients with new and active tuberculosis examined at a county tuberculosis clinic, 67 per cent were referred by a physician and 30 per cent by all other organizations and departments of health. It was found on study of the cases that, as compared with the results of examining contacts, physicians refer more patients with the active condition per hundred persons examined; a high percentage of their patients come to the clinic in an early stage of the disease, and the cost per patient is lower in their group.

EUGENE H. SMITH, Ogden, Utah.

CASE FINDING. W. H. HATFIELD, Am. Rev. Tuberc. **41**:748 (June) 1940.

A primary requisite of effective case finding is a well regulated and efficiently operated health department to which patients and medical practitioners may turn for any diagnostic aid necessary. Such an organization appears to be functioning in British Columbia. In this paper Hatfield discusses the efficiency of the various

methods used. Tuberculin tests of large groups of school children were disappointing from this standpoint. But 35 cases of tuberculosis among 4,136 positive reactors were discovered by this method among 21,358 children in three years, or 12 new cases annually; this was a very small percentage of the total new cases found in the general population during this time. Home follow-ups, moreover, showed practically no new cases of tuberculosis. The benefit of this procedure seems to lie chiefly in its value from an educational standpoint.

Contact work should occupy the chief place in case finding. But to be effective this requires carefully coordinated team work between the physician, the public health nurse and the social worker. Special attention should be paid to such occupational groups as teachers, nurses and miners. An age group which deserves more consideration than it usually receives is that between 40 and 60 years. During 1938, 36.3 per cent of new patients were in this group.

All "contacts" should have an adequate roentgen study. Perhaps fewer hastily made examinations in younger groups, with concentration on the age groups in which the most cases are found, would save expense and detect more cases.

Examinations of the sputum should be made more frequently, and adequate laboratory facilities should be available to all practitioners.

The family physician is vital to a successful control program, and his cooperation should be encouraged in every way. His contacts with families could be made to supply a most valuable element in case finding.

EUGENE H. SMITH, Ogden, Utah.

MORPHOLOGICAL VARIATION OF THE TUBERCLE BACILLUS AND CERTAIN RECENTLY ISOLATED SOIL ACID FASTS, WITH EMPHASIS ON FILTRABILITY. HARRIETTE D. VERA and LEO F. RETTGER, J. Bact. **39**:659 (June) 1940.

There has always been a controversy in regard to the possible significance of various forms of the tubercle bacillus in the etiology and prognosis of tuberculous infection. Investigators seem to agree that the Koch bacillus does not necessarily have to appear in the classic rod shape at all times. A granular rod, coccoid bodies, filaments and clubs have been observed. The question of the existence of filtrable forms has arisen. The authors attempted to answer this question. They obtained various strains of mycobacteria and made a careful study of them. In conclusion they feel that there is no evidence for the existence of filtrable forms of Mycobacterium tuberculosis and other mycobacteria. They could produce many cell forms by employing mediums poor in nutriment and by reducing oxygen tension. They observed that the common method of reproduction of the tubercle bacillus was division. Occasionally branching occurred. Further studies are indicated, for the last word concerning the gross morphology of the tubercle bacillus has not yet been said. STOESSER, Minneapolis.

COMPARATIVE VALUE OF LEVINSON AND TRYPTOPHANE TESTS IN THE DIAGNOSIS OF TUBERCULOUS MENINGITIS. MORRIS GLEICH and ROSLYN WEINTRAUB, Arch. Pediat. **56**:749 (Nov.) 1939.

The Levinson test has been helpful in the diagnosis of tuberculous meningitis. The authors have endeavored to compare the relative value of the Levinson and the tryptophan tests.

The Levinson test gave positive results in 100 per cent of the cases of tuberculous meningitis and negative in all nontuberculous cases.

The tryptophan A test gave positive results in 89 per cent of the cases of tuberculous meningitis but also gave positive results in 100 per cent of the cases of nontuberculous meningitis. The tryptophan B test gave positive results in 66.6 per cent of the cases of tuberculous meningitis but also gave positive results in 38.5 per cent of the nontuberculous cases. ORR, Buffalo.

THE PROGNOSIS OF INFANTILE TUBERCULOSIS. CLEMENT A. SMITH and WINIFRED DELACEY, New England J. Med. **222**:213 (Feb. 8) 1940.

In the fifteen year period from the beginning of 1924 to the end of 1938, 339 infants with some form of tuberculosis were seen in the hospital, and of this number 191 (56 per cent) died there. Of the remaining 148 infants only 116 could be traced satisfactorily. Of these, 41 died within a year after discharge from the hospital and 1 after eighteen months. Of those still alive, 6 have foci which persist; 1 has tuberculous cervical adenitis; 2 have cervical adenitis and skeletal tuberculosis; 2 have skeletal tuberculosis only, and 1 (at the age of 14 years) has minimal adult type tuberculosis.

GENGENBACH, Denver.

THE PREVENTION AND CONTROL OF TUBERCULOSIS IN MASSACHUSETTS. FREDERICK T. LORD, New England J. Med. **223**:5 (July 4) 1940.

In a total school population of 73,851 children, 45,343 (61 per cent) were tested with tuberculin, and 9,730 (21 per cent) gave positive reactions. In the course of the investigation 12,503 children were examined with the roentgen rays. Forty-four cases of the adult type of tuberculosis were found, or about 1 for every 1,000 tuberculin-tested children and 1 for every 221 reactors. The childhood type of tuberculosis was discovered in 1,083 children, or 1 in every 42 tuberculin-tested children and 1 in every 9 reactors.

Nursemaids and other domestic servants in homes where there are children should have a roentgen examination prior to employment for the purpose of protecting those with whom they come in contact. All school teachers and other employees in contact with children should be examined for tuberculosis for the protection of children.

In considering the responsibilities of the tuberculosis associations, the author suggests that their funds can be used to better advantage for health education; for the promotion of case finding, hospitalization and the breaking of contact; for rehabilitation, and for the investigation of local needs with regard to tuberculosis.

GENGENBACH, Denver.

TROCHANTERIC TUBERCULOSIS (CURE IN TWO MONTHS BY EXCISION AND OSSEOUS GRAFT). AKIF CHAKIR, Rev. d'orthop. **25**:648 (Nov.) 1938.

The author reports 1 case of intertrochanteric tuberculous abscess of the femur. Rapid healing followed excision of the abscess cavity and the placing of a bone graft in the defect.

This article leaves the reviewer in doubt as to the cause of the osseous abscess.

TURNER, Evanston, Ill.

TEN YEARS OF VACCINATION WITH BCG IN NORRBOTTEN (SWEDEN). CARL NAESLUND, Rev. de la tuberc. **5**:710 (June) 1939.

Norrbotten (Sweden) was chosen for this study because for a long time tuberculosis had been prevalent in this region and unusual difficulties had attended the medicosocial control of the disease. Vaccination of the newborn was not compulsory, although parents were urged to consent to the procedure. Most infants were not removed from their usual environment. Vaccination was done according to the original Calmette method of oral administration of three doses of BCG. During the ten year period 13,103 infants born in this region were vaccinated and 34,845 were not.

In a study of this kind it is obviously difficult to obtain exact information on causes of death. However, from year to year greater accuracy in this respect has been forthcoming, so that the figures regarding the mortality from tuberculosis may be regarded as having definite importance.

During these ten years, the deaths from all causes among the vaccinated were 6.1 per cent and among the unvaccinated 11.17 per cent. If deaths occurring during the first five days of life are disregarded, the figures are 5.96 and 9.53 per cent respectively. According to age at the time of death, the mortality rates for the first year were: vaccinated children, 5.97 per cent; nonvaccinated children, 9.71 per cent. For the second year these rates were 0.92 and 1.23 per cent respectively, and for the third year, 0.45 and 1.52 per cent respectively. During the succeeding years there were no significant differences in mortality between the two groups.

The reasons for the differences just given have been the subject of much discussion. Some have held that the vaccination itself was responsible. Naeslund feels that this position is not tenable and that the difference is due to a combination of many factors, economic, medical and social. Likewise, the view held by some that vaccination with BCG produces a certain nonspecific immunity against infections in general is not supported by Naeslund's observations.

For the ten year period, the number of deaths from tuberculosis among the vaccinated was 1.5 per thousand and that among the nonvaccinated was 6.3. The mortality from tuberculosis for different ages ranged from 4.1 per thousand among vaccinated and 23.1 per thousand among nonvaccinated for those in the first year, to 0.9 among vaccinated and 3.6 among nonvaccinated for the 4 to 5 year age group. After the sixth year there were no deaths from tuberculosis in the vaccinated group. These figures, based on reports of the medical officials, indicate that deaths from tuberculosis were four times as numerous among the nonvaccinated as among the vaccinated.

EUGENE H. SMITH, Ogden, Utah.

VACCINATION WITH BCG BY CUTANEOUS SCARIFICATION. B. WEILL-HALLÉ, Rev. de la tuberc. **5**:827 (July) 1939.

In this procedure two sets of three scratches are made at right angles to each other on the skin of the arm, through a drop of BCG. Within two or three weeks a slight infiltration of the skin appears, resembling that produced by a positive reaction to a tuberculin cutaneous test. The appearance of this local reaction seems to be accelerated when the subject has previously been vaccinated but has lost his sensitivity to tuberculin. Further observation is necessary to determine the degree and duration of the immunity produced by this method.

EUGENE H. SMITH, Ogden, Utah.

VACCINATION AGAINST TUBERCULOSIS WITH PETRAGNANI'S ANATUBERCULIN. C. TORRICELLI and M. DEPIETRI, Lattante **11**:141 (May) 1940.

Petragnani's anatuberculin is prepared from thirty-three strains of human tubercle bacilli grown on malachite green mediums and treated with solution of formaldehyde. For vaccination four intradermal injections are given in the forearm.

One hundred and twenty-six children under 4 years of age, either foundlings or children with tuberculous parents, were thus vaccinated. Seventy to 80 per cent showed positive tuberculin reactions six months later. Of the 14 deaths, but 1 was due to tuberculosis. Roentgenograms, physical development, autopsy studies and studies of the blood, including sedimentation rates, all point to the safety of this procedure for anergic infants. Vaccination with anatuberculin is worth trying for producing immunity to tuberculosis.

HIGGINS, Boston.

ALLERGY AND IMMUNITY (IATHERGY) IN EXPERIMENTAL TUBERCULOSIS: V. VARIATIONS IN THE LEUKOCYTES IN BCG-IMMUNIZED GUINEA PIGS REINFECTED IN THE ALLERGIC AND THE DESENSITIZED (IATHERGIC) STATE. K. BIRKHAUG, Acta pædiat. **26**:66, 1939.

The work of numerous investigators has demonstrated a correlation between various stages or aspects of tuberculous infections and the leukocyte formula of

the circulating blood. In this respect the monocyte has assumed the most important single role; in general, the ratio between the monocyte and the lymphocyte concentration affords a reliable index of the organism's primary cellular resistance to the infection. Of the numerous leukocytic indexes that have been proposed, the one of Medlar's collaborator, Crawford, exhibits the greatest ingenuity: It consists of the polymorphonuclear neutrophil-lymphocyte ratio plus the abnormal monocyte concentration plus the abnormal total leukocyte count.

The experiments described in this paper were designed to examine the role played by allergy in the pathogenesis of experimental tuberculosis in guinea pigs and also to clarify the significance of the blood count in interpreting the course of tuberculous infection.

Eighty-four normal guinea pigs were divided into three equal groups. The members of group 1 were immunized with a subcutaneous dose of BCG and then inoculated with bovine tubercle bacilli of high virulence. The members of group 2, the so-called iathergic group, were immunized and then desensitized by repeated injections of tuberculin before being inoculated with virulent organisms. The members of group 3, the control group, were inoculated with virulent tubercle bacilli without preliminary immunization. It is of great interest that the animals that were both immunized and desensitized were more effectively protected against progressive tuberculosis than were those which were simply immunized and permitted to retain the accompanying allergy. This finding constitutes confirmation of the conception of Rich and others that allergy is not necessarily a beneficial component of immunity in tuberculosis.

The author summarizes his hematologic findings in the following words: "Carefully controlled studies were made of the leukocytic reactions in BCG-immunized guinea pigs infected with virulent bovine tubercle bacilli and subsequently allowed to remain in the allergic or the completely desensitized iathergic state. The following significant changes were noted:

"1. No clear-cut deviations in the total leukocyte counts were observed to justify the claim that the variations in leukocytosis alone is a reliable indicator of the degree of tuberculous activity.

"2. The monocyte-lymphocyte ratio is a more sensitive and reliable indicator of tuberculous activity than the neutrophile-lymphocyte ratio and the neutrophile 'shift to the left.'

"3. The leukocytic index is a valuable aid to accurate interpretation of the leukocytic reactions in terms of favourable or unfavourable pathological activity.

"4. The monocyte-lymphocyte ratio and the leukocytic index furnish reliable evidence that the abolition of allergic hypersensitiveness by careful tuberculin desensitization leaves the mechanism of acquired tuberculo-resistance intact and significantly retards the pathological activity of virulent tubercle bacilli."

McCUNE, New York.

COMPARATIVE STUDIES WITH REFINED TUBERCULIN, "TUBERCULIN P. P. D." (PARKE-DAVIS & CO.) AND OLD TUBERCULIN (HOECHST). M. DE MARÉ, Acta pædiat. **26**:285, 1939.

Eight hundred and sixty tests were made of children between 2 months and 15 years of age. The results obtained with the two preparations of tuberculin showed complete agreement. Reactions of excessive severity occurred somewhat more frequently with purified protein derivative than with old tuberculin. Nonspecific reactions were found somewhat less frequently with small doses of purified protein derivative than with old tuberculin. At the higher levels of dosage the incidence of nonspecific reactions was reversed. The conclusion is drawn that purified protein derivative is a dependable reagent for tuberculin testing.

McCUNE, New York.

ANTITUBERCULOUS IMMUNITY PRODUCED BY BCG VACCINE. J. ZEYLAND and E. PIASECKA-ZEYLAND, Acta pædiat. **27**:393, 1940.

The authors summarize their animal and clinical researches compactly as follows: "1. Experimental research on 50 guinea-pigs shows that, after virulent infection, previously vaccinated animals live much longer (more than four times) than controls (experiment 1), and when killed some time after infection, they present much smaller tuberculous lesions than controls (experiment 2). These researches demonstrate clearly the checking influence of BCG vaccine on experimental tuberculosis. 2. A comparison was made between two groups of children living in tuberculous surroundings, i. e., in contact with a patient with open tuberculosis: the first group (449 children) was vaccinated with BCG, and the second group (122 children) was not vaccinated; the vaccinated group shows a fivefold diminution of tuberculous morbidity and a tenfold diminution of the tuberculosis mortality in comparison with the unvaccinated group."

McCUNE, New York.

A FOLLOW-UP INVESTIGATION OF CHILDREN WITH POSITIVE TUBERCULIN REACTIONS. THREE CASES OF BIOLOGICALLY HEALED TUBERCULOSIS. P. ROSENBERG, Acta pædiat. **27**:452, 1940.

The portion of this report that describes in a preliminary way the results of follow-up examinations of 47 of 70 children treated two to sixteen years before for tuberculosis possesses some statistical value but little clinical importance. Three of the patients who had reacted positively to testing with unspecified amounts of tuberculin thirteen to sixteen years earlier gave negative reactions to the Mantoux test with up to 1 mg. of tuberculin in 1939. All had shown roentgen evidence of tuberculous infection when originally hospitalized; films of the chest revealed normal features at the time of the follow-up examination. A brief discussion of possible explanations leads to the conclusion that the 3 patients represented examples of complete healing of tuberculosis, with eradication of all foci from the body.

McCUNE, New York.

Diseases of Blood, Heart and Blood Vessels and Spleen

COARCTATION OF THE AORTA IN A CHILD WITH ARRESTED SUBACUTE BACTERIAL ENDARTERITIS AND A CALCIFIED MYCOTIC ANEURYSM AT THE SEAT OF STRICTURE. G. H. B. NICOLSON, Am. Heart J. **20**:357 (Sept.) 1940.

A child with coarctation of the aorta of the adult type had subacute bacterial endocarditis at the age of 10 years. Two blood cultures were positive for Streptococcus viridans. Many embolic phenomena occurred. After an illness of seven months the patient became free from symptoms and has remained well for two years. Following the bacterial infection, a mycotic aneurysm, with calcification of its walls, developed in the descending arch of the aorta.

GIBSON, Chicago.

ORTHOSTATIC PAROXYSMAL AURICULAR TACHYCARDIA WITH UNUSUAL RESPONSE TO CHANGE OF POSTURE. M. J. FINE and R. MILLER, Am. Heart J. **20**:366 (Sept.) 1940.

A case is reported of auricular paroxysmal tachycardia in a 16 year old girl. The tachycardia was always present when the patient assumed the sitting or the standing position unless it was controlled by digitalis or quinidine sulfate. When the patient was recumbent, normal sinus rhythm was sometimes present; at other times the auricular tachycardia persisted. The rate of the tachycardia was influenced by the position of the patient. It was slower in the sitting than in the standing position and slower still when the patient was lying down.

GIBSON, Chicago.

A Comparison of Methods Used in the Detection of the Sickle-Cell Trait. L. W. Diggs and V. D. Pettit, J. Lab. & Clin. Med. **25**:1106 (July) 1940.

The authors have compared five methods now recommended for the detection of the sickle cell trait. These five methods are: moist preparation, gas chamber method, moist stasis preparation, test tube method and moist preparations plus dyes. After trying each method in a number of cases they concluded that the moist stasis method of Scriver and Waugh is the most reliable and practical one.

Gard, Galveston, Texas.

Acute Endocarditis Due to an Anaerobic Pneumococcus. Alvin Hollander and Eva Landsberg, J. Lab. & Clin. Med. **26**:307 (Nov.) 1940.

The authors report a case of endocarditis and meningitis in a 9 year old boy. The causative organism was an anaerobic pneumococcus of a new serologic type, and the isolated organism in this case was not pathogenic for mice. The child was treated unsuccessfully with sulfapyridine administered orally and sulfanilamide administered intrathecally.

Gard, Galveston, Texas.

Modified Technique for Prothrombin Determination in Blood. H. S. Holmboe and R. W. Holmboe, J. Lab. & Clin. Med. **26**:408 (Nov.) 1940.

A readily adaptable method for the determination of prothrombin time which is economical, accurate and simple is described. The reagents, especially the sheep brain thromboplastic agent, are more stable than those used in some of the other methods. This new method has been tried clinically.

Gard, Galveston, Texas.

The Diagnosis and Surgical Therapy of Patent Ductus Arteriosus. John C. Jones, Frank S. Dolley and Lewis T. Bullock, J. Thoracic Surg. **9**:413 (April) 1940.

Successful ligation of the patent ductus arteriosus in 7 patients is reported, with an addendum listing an additional 6 ligations. This operation was first accomplished successfully by Gross and Hubbard in 1938. The youngest patient was a child aged 4 years; the oldest, a 31 year old woman.

All patients had typical physical signs and laboratory evidence of patent ductus arteriosus, with a continuous murmur in the pulmonic area, varying in intensity during each cardiac cycle and usually accompanied by a thrill, reported as the most important sign. Increase of the pulmonary second sound, prominence of the pulmonary conus on roentgen examination, absence of cyanosis, increase in pulse pressure with low diastolic pressure and absence of cardiographic evidence of axis deviation were reported as confirmatory findings.

An anterior approach was used, with positive pressure anesthesia. The ductus was isolated and ligated according to the principles involved in the ligation of large arteries. The postoperative courses were uneventful. There was 1 delayed death, and temporary hoarseness was noted in 2 cases. Postoperative care in regard to fluids is of especial importance.

There follows a significant discussion regarding associated cardiac anomalies. This is a very important contribution.

Dorsey, Chicago.

Production of "Prothrombin Deficiency" and Response to Vitamins A, D and K. Margaret C. Elliott, Bertha Isaacs and A. C. Ivy, Proc. Soc. Exper. Biol. & Med. **43**:240 (Feb.) 1940.

Adding 20 per cent liquid petrolatum to the diets of rats caused hemorrhagic tendencies associated with increase in the prothrombin time. Vitamin K admin-

istered subcutaneously corrected the prothrombin deficiency. Vitamin A had no effect in the deficiency, while activated ergosterol definitely improved the deficiency.

HANSEN, Minneapolis.

SUBSTANCE IN KIDNEYS AND MUSCLE ELICITING PROLONGED REDUCTION OF BLOOD PRESSURE IN HUMAN AND EXPERIMENTAL HYPERTENSION. I. H. PAGE, O. M. HELMER, K. G. KOHLSTAEDT, P. J. FOUTS, G. F. KEMPF and A. C. CORCORAN, Proc. Soc. Exper. Biol. & Med. **43**:722 (April) 1940.

Extracts prepared from fresh pork kidneys and from muscle of rat, rabbit and beef were extracted with various solvents, concentrated and dialyzed, passed through Seitz filters and then injected intramuscularly into dogs, rats and certain human subjects. Filtrates from the isoelectric precipitation of saline extracts of kidney seemed most effective in decreasing hypertension in rats and dogs. Eight patients were treated with extracts, and in all a sharp prolonged fall in arterial pressure occurred, with symptomatic improvement in each. After administration of the extracts had been stopped for three to five days the blood pressure rose again. These extracts also reduced the ability of the plasma to activate rennin and angiotonin. In 4 dogs suffering from malignant hypertension injection of these tissue extracts caused a drop in blood pressure, with improvement in the signs in the eyegrounds. In 2 human subjects with malignant hypertension, a striking fall in blood pressure with an increase in the urea clearance tests occurred when the extracts were injected. The authors state that it is too early to assert that over prolonged periods these extracts will have therapeutic value; however, animal tests suggest that they may have value.

HANSEN, Minneapolis.

USE OF SODIUM HEXAMETAPHOSPHATE AS AN ANTICOAGULANT. C. E. LARSON, Proc. Soc. Exper. Biol. & Med. **44**:554 (June) 1940.

Sodium hexametaphosphate $(NaPO_3)_6$ or $(Na_6P_6O_{18})$, which reacts with the calcium ion to form $Na_2Ca_3P_6O_{18}$, has been used in industrial chemistry, especially as a water softener. The author found this substance to be an anticoagulant and possibly to have certain advantages over existing agents.

HANSEN, Minneapolis.

GENERALIZED ANGIOMATOSIS PRESENTING THE CLINICAL CHARACTERISTICS OF STORAGE RETICULOSIS. LEONARD G. PARSONS and J. H. EBBS, Arch. Dis. Childhood **15**:129 (Sept.) 1940.

A clinical and pathologic report is given of a 14 year old girl who showed clinical evidence of the "osseous form of Gaucher's disease" but who at post-mortem examination was found to have suffered from cavernous angiomas of varying size in the liver, spleen, retroperitoneal glands, thymus, mediastinum, lungs, pleura, kidneys and most of the bones of the body. The case is a difficult one to classify because of the widespread involvement of reticuloendothelial tissue, although histologically it was apparently an example of multiple hemangiomas the cells of which had benign histologic characters. A discussion of the relation of this condition to "reticulosis" and reticuloendotheliosis is included.

KELLY, Milwaukee.

SOME OBSERVATONS ON CHANGES IN THE MINERAL CONTENT OF PLASMA AND SERUM. B. SPLATT, M. J. Australia **2**:363 (Oct. 19) 1940.

In confirmation of the conclusions of other workers, the potassium content of the plasma was observed to increase during storage. The increase commences as soon as the shed blood is mixed with the anticoagulant solution. The chloride and sodium content of the plasma decreases, while the calcium and magnesium content increases somewhat irregularly. These changes are minimal in the dextrose-citrate anticoagulant solution of Duran-Jorda. No significant changes were

observed in the mineral constituents of the serum obtained after hemorrhage. The administration of large amounts of potassium in transfusions of stored blood or serum does not cause any significant rise in the potassium content of the serum obtained from the recipient after this treatment. The absence of toxic effects after these large doses of potassium is attributed to the presence in sufficient amounts of neutralizing sodium ions in the stored blood or serum and to the slow rate of transfusion.

GONCE, Madison, Wis.

TOTAL BLOOD VITAMIN C CONTENT IN HEMORRHAGIC DIATHESIS AND THE EFFECT OF ASCORBIC ACID ON BLEEDING TENDENCIES AND BLOOD. F. KOSAKI, Acta pædiat. japon. **46**:768 (July) 1940.

In various types of hemorrhagic disease (6 cases of symptomatic thrombopenic purpura, 1 of idiopathic thrombopenic purpura, 2 of hemophilia, 1 of acute myelogenous leukemia and 1 of aplastic anemia) the total vitamin C content of the blood was found to be 1 to 1.4 mg. per hundred cubic centimeters. In the cerebrospinal fluid the amounts varied from 1.4 to 1.8 mg. per hundred cubic centimeters, while the vitamin C content of the urine was materially decreased. Intravenous or subcutaneous injections of ascorbic acid in large doses over a period of one week caused no appreciable alteration in either the bleeding tendencies or the number of circulating platelets. Only in 1 instance of symptomatic thrombopenic purpura was an increase in the number of blood platelets observed. There was also a slight improvement in patients with hemophilia under this treatment, although the urinary excretion of the vitamin was consistently low.

KATO, Chicago.

TWO CASES OF SPLENIC CONTROL OF THE CELL EMISSION FROM THE BONE MARROW. JAN SCHONBOE, Acta med. Scandinav. **103**:123, 1940.

The first patient suffered from lymphogranulomatosis. Enlargement of the spleen and the hilus glands with anemia and leukopenia constituted the pathologic findings. The spleen was removed, and the patient died of pneumonia sixteen days after the operation. The bone marrow showed hyperplasia. The second patient was a 16 year old girl with congenital syphilis. She had syphilitic osteitis of several long bones, with a huge spleen and liver. Antisyphilitic treatment healed the osseous lesions and reduced the size of the spleen and liver, but two years later she was readmitted with recurrent hematemesis and ecchymoses. During the periods of bleeding the size of the spleen diminished. Examination of the blood showed leukopenia, with a normal differential count. No nucleated red blood cells were found, although the value for hemoglobin was as low as 28 per cent. Puncture of the sternal bone marrow showed a normal formation of the cells. Splenectomy was performed. The spleen was adherent. For sixteen months the girl enjoyed fair health, and the peripheral blood picture returned to normal. Then recurrence of hematemesis proved fatal. Before death the patient had leukocytosis and 20 per cent reticulated red blood cells; 34 per cent of all nuclear cells were normoblasts. The bone marrow showed hyperplasia. This second case is especially instructive. While before splenectomy no nucleated red blood cells got into the circulation in spite of hyperplasia of the bone marrow, after splenectomy the peripheral blood was flooded with normoblasts. The author regards these cases as indicative that if some substance formed in the spleen reaches the circulation without passage through the liver by collateral vessels the emission of blood cells from the bone marrow will be inhibited.

KAJDI, Baltimore.

ACUTE LEUKEMIA AND ACHRESTIC ANEMIA IN A BROTHER AND SISTER. J. BICHEL, Acta med. Scandinav. **104**:578, 1940.

The author reports a case of acute leukemia in a young woman. The immature cells cultivated in vitro were capable of maturing into myelocytes. At the same

time her brother was treated for "achresthic anemia," i. e., the blood picture corresponded to pernicious anemia, but there was no paresthesia or glossitis, and treatment with liver extracts, vitamin B preparations and iron was ineffective. The author regards the condition as a kind of aplastic anemia. The relation between aplastic anemia and acute leukemia and the question of hereditary predisposition are discussed.

KAJDI, Baltimore.

THE MALIGNANT FORM OF GAUCHER'S DISEASE. C. DE LANGE, Acta pædiat. **27**:34, 1939.

In this communication are reported 2 cases of Gaucher's disease in which the patients died of the disease itself, not of intercurrent infection, during the first year of life. The patients were a sister and a brother. The sister was not observed by physicians; the diagnosis of her illness and the cause of death was made when the brother was brought for medical attention because of symptoms similar to hers, namely, paroxysmal cough and evidence of cerebral disturbance. In addition to pathologic signs of extrapyramidal origin and mental retardation, the boy showed enlargement of the liver and spleen and a myelophthisic blood picture. Dysphagia and cachexia developed, and death ensued. The clinical diagnosis of Gaucher's disease was confirmed histologically and received chemical support. Although the brain was not examined, the author voices the surmise that the nervous manifestations were due to extension of the Gaucher lesions to the cerebrum. The literature is reviewed with especial attention to the hypothesis that the uncommon malignant form of Gaucher's disease occurring in infancy bears the same relation to the more benign form observed in adults that the Tay-Sachs syndrome occupies with respect to the Niemann-Pick disease.

MCCUNE, New York.

ACUTE LYMPHATIC LEUKEMIA IN MONOZYGOTIC TWINS: I. REPORT OF A CASE WITH PARTICULAR ATTENTION TO ETIOLOGY. II. ETIOLOGY: CONSTITUTION AND EXTERNAL INFLUENCES. H. JELKE, Acta pædiat. **27**:87 and 137, 1939.

These two papers constitute a monograph on the significance with relation to the etiology of lymphatic leukemia borne by the occurrence of the disease in twins. Jelke takes as his text 2 fatal cases of acute lymphatic leukemia in a pair of monozygotic 6 month old twin girls. Aside from the fact that one of the twins died shortly after the onset of the disease from an intracranial hemorrhage while the other survived long enough to receive roentgen treatment, the disease manifested itself identically in the 2 infants. Both exhibited rapid physical decline, with progressive pallor and splenomegaly. The white blood cell concentration approximated 1,000,000 per cubic millimeter; most of the cells were lymphocytes and lymphoblasts. Puncture of the sternal marrow revealed lymphatic myeloplasia; at autopsy the tissues were found to be infiltrated by cells of the same type.

All theories concerning the etiology of leukemia include a constitutional factor. That such a factor is of importance is revealed by the fact that to date 25 instances of familial leukemia involving 53 patients have been reported. It is of interest that in two thirds of these cases the type was lymphatic, while the so-called "epidemic" leukemia in nonconsanguineous groups is usually myelogenous. Relatives of victims of lymphatic leukemia not infrequently show peculiarities of the leukocyte formula. The simultaneous occurrence of the disease in both members of a pair of uniovular twins has been reported only once before. Although cases of this sort cast no light on external factors, they do throw into relief the importance of constitutional predisposition to the disease.

MCCUNE, New York.

EXPERIMENTS IN THE RESUSCITATION OF THE ISOLATED HEART OF THE CHILD. N. OSSINOWSKY, Acta pædiat. **27**:233, 1939.

The ability to resuscitate the extirpated heart of the dead child is a matter of direct physiologic importance and of some indirect clinical interest. It has been attempted successfully several times in the past, principally by Russian observers. Ossinowsky has succeeded in accomplishing this end in about 50 per cent of 71 efforts. The ability to resuscitate the heart depends somewhat on the age of the subject; the hearts of young children are much more easily caused to beat again than are those of older children. The cause of death is also of importance. The period during which the artificially engendered pulsations can be caused to continue is highly variable and is regulated, among other things, by the carefulness of the experimental technic. The procedure lends itself to the study of the effect of various drugs. Preliminary experiments with epinephrine hydrochloride, atropine sulfate and other substances are reported. McCUNE, New York.

Diseases of the Nose, Throat and Ear

DISCUSSION ON EAR DISEASE IN THE CHILD. A. G. WELLS and PHYLLIS KERRIDGE, Proc. Roy. Soc. Med. **32**:1625 (Oct.) 1939.

Taking up the treatment of aural disease in children, Wells (1) discusses fully diastolization (*a*) by itself, (*b*) with nasal application, (*c*) plus local treatment for otorrhea and (*d*) plus removal of tonsils and adenoids; (2) refers briefly to the treatment of chlorine ionization; (3) states that for catarrhal conditions of the nose, ear and throat local treatment should be combined with general treatment, particularly an increase in raw foods, fruit and vegetables and a corresponding limitation of carbohydrates; (4) says that in cases of chronic suppurative otitis media he employs various treatments, outstanding among which is zinc ionization, and (5) reports that in treating acute inflammation of the middle ear he sends most patients to bed with instructions to rest in the semirecumbent position with a flannel garment covering the head and face completely, keeping it on for forty-eight hours, so that the continuous heat which it causes results in hyperemia and as large a supply as possible of white cells to combat the infection; in some cases, in addition, phenol and glycerin drops are used.

Kerridge states that the Board of Education of England estimated that 80 per thousand school children have defective hearing, but 95 per cent of such children have defects so slight that the term deafness is not suitable and the children do not suffer from any educational handicap. Most of them (98 per cent) need medical care over a long period for their general health. The defects of hearing in these children are due to chronic disease of the middle ear, resulting from scarlet fever or measles. Defective hearing among the elementary school children is four times as common as among children in private schools. Climate does not appear to have as much effect on the condition as was expected.

WILLIAMSON, New Orleans.

Diseases of the Lungs, Pleura and Mediastinum

THE TREATMENT OF PNEUMOCOCCAL PNEUMONIA IN INFANTS AND CHILDREN WITH SULFAPYRIDINE. JOHN A. V. DAVIES, New England J. Med. **221**:734 (Nov. 9) 1939.

In all, 154 patients with pneumococcic pneumonia—71 infants and 83 children—were treated with sulfapyridine. The pneumonia was considered primary in 151 patients.

Material for the typing of pneumococci was obtained by placing a sterile swab deep in the patient's pharynx and inducing a cough.

Among the infants under 2 years of age, for example, type XIV was by far the commonest, types VII, XIX, III and VI and IV and XVII following in that order. In the children over 2 years of age, type I was predominant. Type XIV was the next most frequent, occurring especially among the younger children.

The blood cultures of 13 patients were positive. In no case did the blood culture remain positive for pneumococci after the administration of sulfapyridine.

Of the 71 infants treated with sulfapyridine (including 1 treated twice and 2 readmitted), 57 (80 per cent) became afebrile within forty-eight hours, 19 (27 per cent) in the first twelve hours and 19 (27 per cent) more in the next twelve hours.

An initial dose of ½ grain (0.03 Gm.) of sulfapyridine per pound of body weight, by mouth, followed by small divided doses amounting to 1 grain (0.06 Gm.) per pound per day for children and 1½ grains (0.09 Gm.) per pound per day for those under 2 years of age, usually results in therapeutically effective blood levels (from 4 to 8 mg. per hundred cubic centimeters). The drug should be mixed with some semisolid food. At the outset, inability of the patient to retain the drug by mouth or the severity of the illness may occasionally require the intravenous administration of sodium sulfapyridine (sodium 2-[paraaminobenzenesulfonamide]-pyridine) in a 5 per cent concentration in sterile distilled water, in a dose of ½ grain or 1 grain per pound.

GENGENBACH, Denver.

TREATMENT OF EMPYEMA IN INFANTS. E. ZECCA, Pediatria **47**:885 (Oct.) 1939.

The author reports on 18 patients with empyema. Six were treated medically without operation. Of these, 4 were cured and 2 died. Twelve were treated surgically. Of these, 9 were cured and 3 died. The author concludes that the treatment of empyema is an individual problem and that each case must be studied carefully.

MARTOCCIO, Utica, N. Y.

STAPHYLOCOCCIC EMPYEMA TREATED WITH PRONTOSIL. JOSÉ PERÓBA, Pediat. é puericultura **9**:34 (Sept.) 1939.

The author presents a case of staphylococcic empyema successfully treated with azosulfamide (disodium 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′-6′-disulfonate) injected into the pleural cavity at two or three day intervals. The patient was a 10 month old white child, markedly undernourished, with a high temperature and all the physical signs of a large empyema. It is interesting that this child was treated during the first eight days by repeated punctures, with removal of variable quantities of thick pus. A "colloidal copper solution" of unknown strength was then injected into the pleural cavity. Nevertheless, the clinical picture did not improve until azosulfamide was injected into the pleural cavity and into the muscles. The child was considered cured after fifteen days, when the roentgenograms were apparently normal.

SOTO, Havana, Cuba.

APPLICATION OF SERIAL ROENTGENOGRAMS ACCORDING TO ABREU-HOLFELDER IN PULMONARY DIAGNOSIS IN PEDIATRICS. BENNHOLDT-THOMSEN and W. M. H. WEISSWANGE, Kinderärztl. Praxis **11**:198 (June) 1940.

The technic of Abreu and Holfelder is recommended for roentgen examination of the chests of large numbers of children. The picture (24 by 24 mm.) is taken from the fluoroscopic screen with a Leica or Contax camera. This picture can be easily enlarged with a Leitz "Röntgen-Diagnostor" to 9.5 by 9.5 cm. For large scale examination of school children the advantages of significantly reduced costs are obvious.

HEYMANN, Cleveland.

STUDIES IN PNEUMONIA OF INFANTS: I. CLINICAL AND STATISTICAL SURVEY; II. INORGANIC BLOOD CALCIUM AND PHOSPHORUS. T. OTA, Orient. J. Dis. Infants **27**:109 (March) 1940.

Of 18,517 patients admitted to the pediatric department of Dairen Hospital for a ten year period (1928 to 1937), there were 1,270 (6.9 per cent) in whose cases the diagnosis on admission was primary pneumonia. The mortality rate was 22.8 per cent, the cause of death from the croupous type being usually the complicating empyema. The mortality of rachitic infants was approximately three times higher than that of nonrachitic babies.

Of the 60 infants admitted with the diagnosis of pneumonia, chiefly bronchopneumonic, 26 showed either definite or suspicious roentgen changes in the long bones suggestive of rickets. The mortality for this group of patients was 30.8 per cent, whereas for nonrachitic babies it was only 11.8 per cent. This observation has especial value in the management of rachitic infants with regard to pneumonic infection.

A significant reduction in the inorganic phosphorus content of the blood (average 2.9 mg. per hundred cubic centimeters) and in the calcium content (average 9.9 mg. per hundred cubic centimeters) in the nonrachitic infants during the attack of pneumonia points to a disturbance of mineral metabolism directly attributable to the pneumonic process. This may be an important factor in the high mortality of pneumonia in rachitic infants.

KATO, Chicago.

Nervous Diseases

SULFATHIAZOLE IN STAPHYLOCOCCUS AUREUS EPIDURAL ABSCESS WITH SEPTICEMIA AND PYEMIA. THOMAS S. P. FITCH, Arch. Pediat. **57**:119 (Feb.) 1940.

A 10 year old child presented a spinal epidural abscess caused by Staphylococcus aureus. A laminectomy drained the abscess. The elevated temperature and toxic symptoms, with a blood culture showing fifty colonies of hemolytic Staph. aureus per cubic centimeter, indicated septicemia. Sulfathiazole (2-para-aminobenzenesulfonamido-thiazole) was given in relatively large amounts. Suppurative empyema following metastatic bronchopneumonia with Staph. aureus and a deep abscess of the ankle due to the same organism were successfully drained surgically. The blood stream became sterile, and apparent recovery occurred.

ORR, Buffalo.

DRUG THERAPY IN CASES OF INFANTILE CEREBRAL PALSY AND ALLIED DISORDERS, WITH SPECIAL REFERENCE TO HYOSCINE. IRA C. NICHOLS and SAMUEL R. WARSON, New England J. Med. **221**:888 (Dec. 7) 1939.

"The present therapeutic approach to the problem of the spastic child takes advantage of many forms of therapy, but it is believed that drug therapy has not received adequate trial.

"A few carefully studied patients were placed on hyoscine hydrobromide. The usual maintenance dose was $\frac{1}{200}$ grain given twice daily by mouth. The response was most encouraging in that drooling was stopped, athetosis lessened, confidence increased, relaxation improved and progress in retraining became more rapid. One child learned to walk in three days.

"No general contraindications to hyoscine were established. In particular, there were no increasing tolerance, no annoying side effects and no untoward symptoms even when the drug was suddenly withdrawn after periods as long as nine months.

"The favorable response to hyoscine came early or not at all. Benzedrine sulfate, phenobarbital and atropine sulfate were investigated clinically in the same series. The therapeutic results of this part of the study were disappointing."

AUTHORS' CONCLUSIONS.

A Study of Chorea with Special Reference to Rheumatic Chorea. S. N. Senn, Indian J. Pediat. **7**:135 (July) 1940.

Contrary to previous opinions, chorea is by no means rare and must be considered a potent cause of heart disease in India.

The exact mechanism of the involuntary movement is not clearly known. It involves a wide area of the nervous system, including the cerebrum, the nerve cells and fibers of the corpus striatum, the cerebellum and the mesencephalon. These areas may be injured by rheumatic toxin, as in Sydenham's chorea; by the virus of encephalitis epidemica, as in encephalitic chorea, and by degenerative changes, as in Huntington's chorea.

In a well developed case there are irregular and involuntary movement, muscular weakness and emotional instability. The reflexes are usually normal. Fever indicates a rheumatic complication.

Three case histories are accompanied by some excellent photographs showing the typical expression and the "choreic hand." Tenney, Madison, Wis.

Treatment of Epilepsy with Sodium Diphenyl Hydantoinate. Denis Williams, Lancet **2**:678 (Sept. 23) 1939.

Ninety-one patients with chronic epilepsy who had ceased to respond to other anticonvulsive agents were treated with sodium diphenyl hydantoinate.

The convulsions were reduced in frequency in 79 per cent of the subjects with grand mal and in 63 per cent of those with petit mal. In 19 per cent the improvement was dramatic. Toxic symptoms arose in 36 per cent, and 2 patients died in status epilepticus while receiving the drug. The author cautions that administration of the drug requires careful observation of the patient.

Langmann, New York.

Pfeiffer's Meningitis. Donald Paterson, Proc. Roy. Soc. Med. **33**:372 (May) 1940.

The case of a boy of 1½ years is reported. He was treated with sulfanilamide for seven days and then with sulfapyridine for three days. Sulfanilamide was given again for five days and an intramuscular injection of sulfapyridine about a week later. The dose was gradually increased for six days and then gradually decreased; it was discontinued about three days later. The child did not respond well; he had remittent fever, and the pulse remained high. Twelve days later the temperature became normal. On admission the spinal fluid was turbid, with no organisms and a negative culture. Two days before the temperature fell to normal the fluid was cloudy. A smear showed pus and gram-negative bacilli, and five days later the smear showed the same. Williamson, New Orleans.

Acute Pseudomeningococcus Meningitis. M. L. and F. Chevrel, Paris méd. **2**:295 (Dec. 2-9) 1939.

The authors report a case of meningitis due to Micrococcus catarrhalis in a child 4 years of age which responded favorably to sulfapyridine given intramuscularly. Leslie, Evanston, Ill.

The Palm-Chin (Marinesco-Radovici) Reflex in the Child. M. Schachter-Nancy, Rev. franç. de pédiat. **13**:180, 1937.

The reflex described by Marinesco and Radovici in 1920 consists of the contraction of muscles in the region of the chin following mechanical or thermal stimulation of the thenar or hypothenar eminences on the same side. In the normal subject the reflex is brusque and brief; in the subject with a pyramidal lesion it is slower and lasts longer. Studies are cited stating that it is present in 75 per cent of infants under 1 month of age, 90 per cent of those between

1 and 6 months and 50 per cent of those between 6 months and 2 years (the same incidence noted for adults). The author studied the reflex in 1,207 normal children between 6 and 12 years of age. It was positive in 33 per cent of the boys and 21 per cent of the girls.

LESLIE, Evanston, Ill.

PARATYPHOID B BACILLUS MENINGITIS IN AN INFANT. E. G. CASELLI and C. T. TEOBALDO, Arch. argent. de pediat. **12**:416 (Oct.) 1939.

The authors report the occurrence of this condition in a child aged 14 months, who was suffering from urinary infection. This infection was septic and terminated in meningitis.

The colon bacillus was found in the urinary tract, and paratyphoid B bacillus was found in the spinal fluid. It is believed that the colon bacillus is capable of producing two types of toxin: an endotoxin, enterotropic and hepatotropic, which causes the gastrointestinal symptoms, and an exotoxin, neurotropic, which causes the nervous manifestations in the case of urinary infection.

The authors believe that the meningitis from which this child suffered was due to paratyphoid bacillus B.

SCHLUTZ, Chicago.

EFFECT OF THE NEW ANTICONVULSIVE EPANUTIN [SODIUM DIPHENYL HYDANTOINATE]. A. K. A. GYSBERTI HODENPYL, Maandschr. v. kindergeneesk. **9**:252 (March) 1940.

Sodium diphenylhydantoinate has been given to children with recurrent convulsions. The treatment lasted about three months, the smallest quantity given daily being 50 mg. and the largest 400 mg. Six children no longer suffered from attacks; in 1 case the attacks occurred now and then, perhaps because the daily dose was too small. In the other 3 children no effect of the drug was seen on the number of convulsions. Five children showed transitory symptoms of intoxication, such as dulness, vomiting, diarrhea, dizziness and an exanthem resembling urticaria.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of the Genitourinary Tract

PRECIPITIN STUDIES IN NEPHROSIS AND NEPHRITIS. E. GOETTSCH and J. D. LYTTLE, J. Clin. Investigation **19**:9 (Jan.) 1940.

In the serums of 23 patients with nephrosis examined during the edematous stage the quantitative precipitin method (*J. Biol. Chem.* **109**:221, 1935) revealed evidence of an altered protein in the albumin fraction, which was usually associated with an altered protein in the globulin fraction.

No relation could be demonstrated between the amount of altered serum albumin and the albuminuria, cholesteremia, edema or susceptibility to superimposed infection.

In the serums of 17 patients with acute glomerular nephritis minimal amounts of altered protein were found in the albumin fraction with rarely any associated altered globulin.

Studies of serums of patients with various other diseases yielded no evidence that severe malnutrition, hypothyroidism or damage to the liver causes serologic changes of the same magnitude as those found in nephrotic patients.

GUEST, Cincinnati.

THE INTRAVENOUS ADMINISTRATION OF SUCROSE SOLUTIONS AS A MEANS OF PRODUCING INTENSE DIURESIS. HENRY F. HELMHOLZ and JESSE L. BOLLMAN, J. Lab. & Clin. Med. **25**:1180 (Aug.) 1940.

The authors have used various solutions with a tonicity equivalent to 20 per cent sucrose to produce diuresis in rabbits. They used sodium sulfate, urea, dextrose and sorbitol in addition to the sucrose, but they found that the 20 per cent

solution of sucrose produced the greatest degree of diuresis. Several of the substances were too toxic for long-continued use. It was also found that sucrose produced histologic changes in the kidneys, but within thirty-nine days the kidney appeared grossly and microscopically normal.

In this experiment the authors gave 100 cc. of the solutions per hour for one hour for a varying number of injections. When they were given for longer periods the factors of water retention and sodium chloride balance entered into the study.

GARD, Galveston, Texas.

PERSISTENT ENURESIS. A. J. HOOD and B. B. MADISON, Wisconsin M. J. **39**:363 (May) 1940.

Enuresis may be classified as follows:

1. Enuresis due to congenital causes:
   1. Phimosis.
   2. Pinpoint meatus.
   3. Stricture of the anterior urethra.
   4. Stricture of the posterior urethra.
   5. Hypertrophy of the verumontanum.
   6. Submucous fibrosis of the vesical outlet.
   7. Spina bifida.
   8. Ectopic ureteral orifices.
2. Enuresis due to congenital causes plus infection:
   1. Vesical disease, i. e., stone, diverticula, infection.
   2. Renal disease.
3. Enuresis due to infection:

In enuresis most cases have a psychogenic basis, but when the condition is persistent there should be a thorough examination. In many cases so-called enuresis has disease of the urinary tract as its basis. Symptoms produced by obstructing lesions are those referable to obstruction of the vesical neck, sepsis and renal impairment.

Obstructing lesions of the urethra and of the vesical neck all produce much the same pathologic changes. Once obstruction has developed, the changes which follow are due to back pressure. Residual urine accumulates and becomes infected. This usually follows an infection of the upper respiratory tract, diarrhea or an acute exanthem.

A reasonably early study before retention and infection have done irreparable damage is urged.

In the study of persistent enuresis, an investigation for residual urine, a careful analysis of the catheterized specimen and a series of excretory urograms are great aids in diagnosis.

Four cases are reported illustrating some of the aforementioned conditions, their study and the results.

JANNEY, Wauwatosa, Wis.

A PRELIMINARY OBSERVATION ON GONOCOCCAL VULVOVAGINITIS IN CHILDREN IN BENGAL. CHUNI LAL MUKHERJEE, J. Obst. & Gynaec. Brit. Emp. **47**:275 (June) 1940.

One hundred and twenty-five children from 5 months to 11 years of age were treated for gonorrheal vaginitis by three different methods: (1) local irrigations, (2) estrogen therapy and (3) combined local treatment and estrogen therapy. Three negative smears at intervals of one week were considered indicative of a cure. With the first method 62.5 per cent were cured, 22.5 per cent relapsed and 15 per cent were unaffected; with the second method 44 per cent were cured, 32 per cent relapsed and 24 per cent were unaffected, and with the third method 84 per cent were cured, 12 per cent relapsed and only 4 per cent were unaffected.

ADAIR and POTTER, Chicago.

PYELOGRAPHY IN THE DIAGNOSIS OF THE POLYCYSTIC KIDNEY. LOUIS A. SURRACO, Rev. méd. latino-am. **25**:144 (Nov.) 1939.

Pyelographic study of the polycystic kidney has revealed to the author special signs causing him to suspect or assert the diagnosis.

One should notice the appearance of the whole picture and the relation and the character of its elements, especially the similarity to the bilateral pyelogram, the smallness of the pelvis and the length and narrowness of the primary calices.

The author has found the following signs of great value:

1. The sign of the "plug," in which a new calix comes out from the interior of the apex, thus reproducing in series the first pyelogram.
2. The sign of the "rosette" on the end of the primary calices (generally the superior or the inferior); multiple projections are formed pointing toward the axis of the calix.
3. The sign of the "half-moon" or "curvature" consists in the concave deformation produced under the calices of the pelvis by the prominence of the cysts, giving the appearance of segments of a circle, of an hour-glass, etc.
4. The sign of "multiple cups" on the apex of the primary or secondary calix.

The diagnosis is evident if all of these signs are found together, especially when that of the "plug" is reproduced in two or more series.

The diagnosis is doubtful when only one of the signs is evident—above all, when the sign of the "plug" is not reproduced in series. DWYER, Kansas City, Mo.

INFECTION OF THE URINARY TRACT IN AVITAMINOSIS—A HEALING WITH HIGH DOSES OF THE ANTIXEROPHTHALMIC FACTOR. G. PETRO, Ztschr. f. Kinderh. **61**:469 (Dec. 22) 1939.

Frontali first demonstrated urinary infections occurring in rats on a diet deficient in vitamin A. The author continued these studies on 10 white rats. The rats were fed a diet free of vitamin A. In addition to general manifestations (cessation of gain in weight and keratomalacia), cystitis and pyelonephritis developed in all rats between the fortieth and the fifty-sixth day. Individual protocols are given. Two rats serving as controls continued on the diet free of vitamin A until death. Four which were given sesame oil free of vitamin A also died. Four were given provitamin A (beta carotene), and 3 of these made a rapid and complete recovery clinically and anatomically; the fourth succumbed, probably to far advanced urinary infection. SIEMSEN, Chicago.

RENAL RICKETS. K. G. KAIJSER, Acta pædiat. **27**:245, 1939.

The report of a case of azotemic, hyperphosphatemic renal rickets of the classic type—as opposed to the more recently described DeToni-Fanconi and Albright-Butler varieties—is prefaced by a textbook review that adds nothing new to the subject. The case is that of a 14 year old girl who exhibited retardation of somatic development from infancy onward. The development of skeletal deformities led to medical examination when she was 13 years of age; at this time albuminuria was discovered and information obtained that indicated the presence of polyuria for some time in the past. The child presented the physical and roentgen features of moderate rickets. The blood pressure was normal. The volume of the urine was increased and the specific gravity consistently reduced; the reaction was acid; moderate albuminuria was present, accompanied with a small number of leukocytes and a few red blood cells in the urinary sediment. The value for serum calcium varied between 5.5 and 10.9 mg. per hundred cubic centimeters, and that for serum inorganic phosphorus, between 5.0 and 10.4 mg. The nonprotein nitrogen was greatly increased, the highest value obtained being 177 mg., and the lowest, 87 mg., per hundred cubic centimeters. The renal lesion appeared to con-

sist of hypoplasia of the right kidney and a ureteral obstruction on the left side. Numerous supplementary examinations were made. The electrocardiogram showed prolongation of the systole, such as is observed in cases of infantile tetany. The Hamilton test, twice repeated, failed to indicate an increased concentration of parathyroid hormone in the circulating blood. Tests of the dextrose tolerance failed to produce glycosuria. Serial twenty-four hour measurements demonstrated diminution of the excretion of chloride and of phosphorus in the urine. Hourly determinations of the inorganic phosphorus content of the serum on several occasions yielded no important information. The basal metabolic rate was considerably lowered. In view of the hopeless character of the disease, aggressive therapy was not attempted; the patient's health continued to decline progressively up to the time of the preparation of the report.

McCUNE, New York.

Diseases of the Ductless Glands; Endocrinology

TERATOMA OF THE PINEAL BODY: A CLINICOPATHOLOGIC REPORT. BEN W. LICHTENSTEIN, Arch. Neurol. & Psychiat. **44**:153 (July) 1940.

This is the second case on record of teratoma of the pineal gland in the female. The growth was a large tumor compressing the aqueduct of Sylvius. Vomiting and hydrocephalus developed soon after birth. The patient came to autopsy at 6 months of age. (This is case 92 in Bailey, Buchanan and Bucy's "Intracranial Tumors of Infancy and Childhood.")

BEVERLY, Chicago.

A COMPARATIVE STUDY OF THE METABOLIC EFFECTS OF TESTOSTERONE PROPIONATE IN NORMAL MEN AND WOMEN AND IN EUNUCHOIDISM. ALLAN T. KENYON, KATHRYN KNOWLTON, IRENE SANDIFORD, F. C. KOCH and GERTRUDE LOTWIN, Endocrinology **26**:26 (Jan.) 1940.

Intramuscular injections of 25 mg. of testosterone propionate daily or twice daily to a enuchoid person produced reduction in the urinary excretion of nitrogen, sodium, potassium and chloride, together with a gain in weight due largely to water held in association with the salts and protein retained. A considerable reduction in the urinary excretion of inorganic phosphorus accompanied reduction of the other constituents. During recovery sodium, chloride and water were rapidly lost from the body and inorganic phosphorus and potassium less rapidly and less completely, while stored nitrogen was retained in great part for weeks.

Two normal young men responded like the eunuchoids—except that the nitrogen retained (0.03 Gm. per kilogram per day) during the period of maximal effect was half that retained by the eunuchoids.

The 102.7 to 252.2 Gm. of protein estimated as retained by these subjects is not accounted for by increases in the bulk of genital tissues and represents deposit of new material elsewhere in the body. This, together with the reduction in the urinary excretion of inorganic phosphorus, potassium and creatine, points to a somatotropic influence of androgens and provides a clue to the unusual body growth accompanying precocious puberty.

JACOBSEN, Buffalo.

OBSERVATIONS ON THE CONTINUED USE OF MALE SEX HORMONE OVER LONG PERIODS OF TIME. JOSEPH EIDELSBERG and ELLIOTT A. ORNSTEIN, Endocrinology **26**:46 (Jan.) 1940.

In cases of hypogonadism in males in which treatment has been given, there have been almost universally a prompt growth of the penis and scrotum; an increase in pubic hair; an increase in the number, frequency and degree of penile erections and an increase in libido. The present paper deals with the results of prolonged administration of testosterone.

In no case have any ill effects or untoward symptoms or signs appeared. Improvement in general well-being and strength was marked. The mental response and the improvement in outlook were excellent. From the use of about 20,000 mg. no real dangers have as yet made their appearance. It seems that the average maintenance dose may be between 50 and 75 mg. per week but is sometimes more or less. Occasionally treatment may be discontinued without regression. Usually treatment must be continued, just as with other endocrine replacement therapy. There was some rise in the basal metabolic rate in each case, but more interesting was the fact that whereas administration of thyroid had little, or comparatively little, effect early in the course, its effect on the basal metabolic rate was more marked during the periods of administration of testosterone propionate.

JACOBSEN, Buffalo.

PITUITARY FUNCTION IN ADIPOSOGENITAL DYSTROPHY (FRÖHLICH). HERMAN SCHWARZ, ALBERT B. NEWMAN and HARRY BAUM, Endocrinology **26**:605 (April) 1940.

The rise in blood ketones in the rat produced by the injection of serums from patients with Fröhlich's syndrome reveals a tendency (not absolute) toward a greater increase in these ketones than was produced by the serums of normal children. Normal children and those with Fröhlich's syndrome respond essentially in the same way to the administration of insulin and epinephrine and to the Staub-Traugott effect. Demonstrable amounts of gonadotropic principle were not present in the serums of either normal children or those with Fröhlich's syndrome. Administration of anterior pituitary-like gonadotropic hormone in 3 cases produced gonadal development. The obesity was entirely unaffected by such therapy.

JACOBSEN, Buffalo.

VARIATIONS IN THE EFFECTIVENESS OF PERCUTANEOUSLY APPLIED ANDROGENS IN THE RAT. DOROTHY NELSON, R. R. GREENE and J. A. WELLS, Endocrinology **26**:651 (April) 1940.

The relative effectiveness of the various methods of administering testosterone and testosterone propionate to the rat is reported.

JACOBSEN, Buffalo.

STUDIES ON THE INHIBITORY HORMONE OF THE TESTES. BEN VIDGOFF and HERMAN VEHRS, Endocrinology **26**:656 (April) 1940.

Evidence has been obtained indicating the inhibitory effect of an extract of the testes of bulls on the pituitary, thyroid and adrenal glands of rats.

These changes are compared with those induced by estrone and testosterone under similar conditions, and their significance is discussed.

JACOBSEN, Buffalo.

THE RELATION OF THE ANTERIOR PITUITARY TO BILE PRODUCTION. O. B. HOUCHIN and C. W. TURNER, Endocrinology **26**:821 (May) 1940.

In guinea pigs an injection of an extract of the anterior lobes of the pituitary glands of sheep caused a rise in the secretion of bile lasting from four to eight hours.

JACOBSEN, Buffalo.

STILBESTROL, A SYNTHETIC ESTROGENIC PREPARATION. SHELDON PAYNE and E. KOST SHELTON, Endocrinology **27**:45 (July) 1940.

The synthetic drug stilbestrol (4,4-dihydroxy-α,β-diethylstilbene) is found to be a potent estrogenic substance, often surpassing natural estrogens in therapeutic effectiveness.

JACOBSEN, Buffalo.

PRODUCTION OF PERSISTENT CHANGES IN THE GENITAL ORGANS OF IMMATURE FEMALE RATS TREATED WITH TESTOSTERONE. HANS SELYE, Endocrinology **27**:657 (Oct.) 1940.

Evidence is presented which shows that in the very immature rat testosterone inhibits uterine development, although at a later period of life this substance is known to exert a marked uterus-stimulating action. The inhibition of organic sexual development caused by testosterone at an early age persists and prevents the onset of puberty in the rat.

JACOBSEN, Buffalo.

THE EFFECT OF ALPHA ESTRADIOL BENZOATE ON THE SKELETAL DEVELOPMENT OF IMMATURE RATS. J. O. ELY and R. LLOYD PHILLIPS, Endocrinology **27**:661 (Oct.) 1940.

The administration of large amounts of estrogens to mice and to immature rats has been reported to produce marked hypermineralization of the skeleton. It was found, however, that amounts of alpha estradiol benzoate sufficient to produce marked effects on the uteri and the ovaries and marked involution of the thymus glands of immature female rats did not produce demonstrable effects on skeletal development.

JACOBSEN, Buffalo.

THE COMPARATIVE ESTROGENIC POTENCY OF DIETHYL STILBESTROL ESTRONE, ESTRADIOL AND ESTRIOL. C. W. SONDERN and J. LEON SEALEY, Endocrinology **27**:670 (Oct.) 1940.

Assayed by oral administration to spayed adult mice, estrone, estradiol and estriol were found to be respectively one sixty-fifth, one twentieth and one tenth as effective as stilbestrol. In rats estrone was one eightieth, estradiol one sixty-fifth and estriol one thirtieth as effective as stilbestrol.

JACOBSEN, Buffalo.

THE RELATIVE POTENCY OF SEVERAL ESTROGENIC COMPOUNDS TESTED ON BABY CHICKS OF BOTH SEXES. S. S. MUNRO and IGOR L. KOSIN, Endocrinology **27**:687 (Oct.) 1940.

Experiments on white leghorn chicks showed that in ascending oviduct-stimulating power, the order of the estrogenic substances in therapeutic use is: estrone, estradiol, estradiol benzoate and estradiol dipropionate.

JACOBSEN, Buffalo.

GROWTH AND DEVELOPMENT OF SIX GENERATIONS OF ALBINO RATS UNDER TREATMENT WITH THYMOCRESCIN. ALBERT SEGALOFF and WARREN O. NELSON, Endocrinology **27**:693 (Oct.) 1940.

The authors were interested in the possibility of securing the same effects with thymocrescin in successive generations as had been obtained by Rowntree and his collaborators with a simple dilute acid thymus extract (Hanson).

A highly purified aqueous thymus extract, thymocrescin, was prepared. Injection of five times the minimum effective dose reported by Asher into six successive generations of albino rats failed to produce any acceleration of growth or development.

JACOBSEN, Buffalo.

PLASMA ELECTROLYTES AS AFFECTED BY INSULIN AND BY VARYING PARTIAL PRESSURES OF ATMOSPHERIC GASES. M. R. ZIEGLER, Proc. Soc. Exper. Biol. & Med. **43**:165 (Jan.) 1940.

Previous studies indicated that some other factor in addition to hypoglycemia plays a role in the mechanism of insulin-induced convulsions. The electrolytes of the plasma were determined before and at regular intervals after the administration of convulsive doses of insulin to fasting unanesthetized dogs in room air and

subsequently in abnormal atmospheres of oxygen, nitrogen and carbon dioxide. These studies suggest that disturbances in the plasma electrolyte patterns do not explain the convulsions induced by insulin.

HANSEN, Minneapolis.

ESTROGENIC THERAPY BY IMPLANTATION OF STILBESTROL PELLETS. C. M. MACBRYDE, H. FREEDMAN, E. LOEFFEL and D. ALLEN, Proc. Soc. Exper. Biol. & Med. **43**:212 (Jan.) 1940.

Hard pellets of diethylstilbestrol dipropionate, weighing approximately 100 mg. each, were implanted in 6 women who had both ovaries removed. To implant a pellet, a small subcutaneous incision was made in the lumbar region, the sterile pellet inserted and the wound closed with a stitch. Within two days the vaginal smears changed. Practically no local reaction occurred. Menopausal symptoms, both psychic and vasomotor, were greatly relieved as long as the pellet remained in place. The average daily absorption per pellet ranged from 0.127 to 0.250 mg., corresponding to a dose of 2,540 to 5,000 international (estrone) units daily. Stilbestrol administered by pellet seems to be five to ten times as effective per unit weight as that given orally or by injection. Repeated tests of liver function, the red blood cells, the hemoglobin, the white blood cells and the platelets showed no variation from normal.

HANSEN, Minneapolis.

THE EFFECT OF TESTOSTERONE PROPIONATE ON POUCH, SCROTUM, CLITORIS AND PENIS OF TRICHOSURUS VULPECULA. A. BOLLIGER and A. CARRODUS, M. J. Australia **2**:368 (Oct. 19) 1940.

Testosterone propionate administered to sexually immature opossums brings about a pronounced response in the pouch, scrotum, clitoris and penis. The lips of the pouch become thickened and puckered, and the scrotum is elongated to a considerable degree, while the clitoris and the penis both undergo hypertrophy.

GONCE, Madison, Wis.

RELATION BETWEEN STRIDOR AND HYPERPLASIA OF THE THYMUS, WITH RESPECT TO A CASE OF RELAPSING HYPERPLASIA OF THE THYMUS. G. DE TONI, Pediatria **47**:941 (Nov.) 1939.

The author presents the case of an infant 44 days old who had stridor from birth. Roentgen examination showed marked thymic enlargement. Roentgen therapy (500 r in five treatments) brought about complete relief from a clinical standpoint and regression in the size of the thymus as shown by roentgen examination. After three months there was a recurrence of symptoms. Roentgen therapy (600 r in six treatments) again brought about improvement. In another two months there was a recurrence. Roentgen therapy (800 r in eight treatments) brought about complete and definite relief. At the end of two years there had not been any more recurrences.

The author discusses the differential diagnosis of stridor.

MARTOCCIO, Utica, N. Y.

Skin Diseases; Allergy

EXPERIMENTS IN POISON IVY SENSITIVITY: EFFECTS OF SPECIFIC INJECTIONS ON THE LEVEL OF SENSITIVITY TO QUANTITATIVE PATCH TESTS AND ON CLINICAL SUSCEPTIBILITY. SOLOMON GREENBERG and ELLA D. MALLOZZI, Arch. Dermat. & Syph. **42**:290 (Aug.) 1940.

A method of cutaneous testing with quantitative dilutions of the excitant and the application of this quantitative method as an objective measure of the level of cutaneous sensitivity before and after the prophylactic injections are described.

A group of specifically treated subjects and a group treated with blank control injections were subjected to fairly massive natural exposures to Rhus toxicodendron during the six weeks following the injections. The natural exposures in the treated and in the control groups were, on the whole, approximately identical. Under the conditions of the experiment there was little difference in the incidence (or severity) of clinical ivy dermatitis in the two groups. Ivy dermatitis developed in 27 per cent of the specifically treated subjects and in 36 per cent of those who received control injections.

It is demonstrated that in a given group the results of patch tests with poison ivy extract are a general index of the incidence of previous and future clinical susceptibility to dermatitis from natural exposures to the plant.

JACKSON, Iowa City.

VERRUCA PLANTARIS. EDWARD A. OLIVER, Arch. Dermat. & Syph. **42**:302 (Aug.) 1940.

In a series of 516 cases in 276 of which the patients were children, various methods of treatment were used. The author states that the method of choice is the use of roentgen rays and of radium. JACKSON, Iowa City.

SULFAPYRIDINE DERMATITIS: REPORT OF TWO CASES. C. G. LAROCCO, Arch. Dermat. & Syph. **42**:341 (Aug.) 1940.

Two cases of dermatitis caused by sulfapyridine are reported. The eruption was morbilliform, generalized, symmetric and macular. The lesions were devoid of the edematous appearance commonly observed with rubeola and of the urticarial phenomena of serum sickness. Twenty-four hours after the administration of this drug was interrupted the rash had practically disappeared, and in less than forty-eight hours the skin was entirely clear. JACKSON, Iowa City.

NICOTINIC ACID IN THE TREATMENT OF ACNE VULGARIS. FRANCIS W. LYNCH, Arch. Dermat. & Syph. **42**:481 (Sept.) 1940.

Nicotinic acid was administered twice daily in the form of 50 mg. tablets to 46 university students who had had no previous treatment for acne or no treatment for at least three months preceding the trial. No other treatment was used, and the students were given no advice as to diet or hygiene. There was improvement in 55 per cent of the cases.

Nicotinic acid cannot be regarded as a cure for acne, nor does the author hold it responsible for all the improvement noted in the group, but it is a simple and apparently harmless drug which seems to help. JACKSON, Iowa City.

RECKLINGHAUSEN'S DISEASE IN IDENTICAL TWINS. EARL L. LOFTIS, Arch. Dermat. & Syph. **42**:657 (Oct.) 1940.

The author reports the cases of identical twins, unmarried women aged 42, who consulted him about an eruption which had been present since the age of 8 years. The condition had appeared simultaneously in both patients and had slowly progressed, new lesions appearing from time to time. The tumors had about the same distribution in the twins and varied from the size of a pinhead to that of a dime. The histologic picture was typical of Recklinghausen's disease.

JACKSON, Iowa City.

AN INQUIRY INTO REAGINS IN CONVALESCENT SERUM INDICATING ITS INHIBITING EFFECT. I. HARRISON TUMPEER, J. Allergy **11**:333 (May) 1940.

The author presents a group of studies to determine the effect on the reagins and allergens contained in convalescent serum when it is diluted, pooled or stored. His conclusions are:

1. Convalescent serum does not yield evidence of reagins, which might be anticipated from the probability that pools include blood serum from allergic persons.

2. Pooled serum to which known highly reaginic ragweed serum has been added likewise fails to disclose ragweed reagins by passive transfer.

3. Further studies indicate that the inhibiting effect is due to the serum rather than the factor of dilution.

4. The inhibiting effect is strongest in stock pools, less strong in fresh pools and least strong in single serum and fresh pools before Berkefeld filtration and treatment with a preservative.

5. The possible therapeutic effect of pooled serums, fluid or lyophilized, is suggested and is being investigated.

HOYER, Cincinnati.

THE USE OF POTASSIUM CHLORIDE IN THE TREATMENT OF ALLERGIC CONDITIONS. W. C. SPAIN, F. HOWARD WESTCOTT and G. EVERETT GAILLARD, J. Allergy **11**:388 (May) 1940.

A group of 31 sufferers from hay fever due to ragweed and a group of 12 patients with allergic coryza were given potassium chloride during the hay fever season. The dose ranged from 15 to 50 grains (0.9 to 3.2 Gm.) daily; the salt was given either in the form of a solution or as capsules, the contents of which were to be dissolved in a glass of water. Fifteen of the sufferers from hay fever were given weekly injections of physiologic solution of sodium chloride in addition to the potassium chloride; 16 were given the salt and regular injections of ragweed extract. Fifty control subjects received the regular injections of ragweed extract.

The authors were disappointed with the results obtained.

HOYER, Cincinnati.

EXPERIMENTAL ALIMENTARY ALLERGY AND ITS PREVENTION. J. BRONFENBRENNER, D. M. HETLER, FRANCES M. LOVE and JACK M. BURNETT, J. Allergy **11**:466 (July) 1940.

A group of experiments were performed on guinea pigs in an attempt to show that a lack of ascorbic acid in the diet increases the permeability of the intestinal mucous membrane. The animals were sensitized to egg white by intraperitoneal injection of 1 cc. of 5 per cent solution.

The authors feel that a lack of vitamin C in the diet increases the permeability of the digestive tract, making possible greater absorption of protein, with subsequent symptoms resembling those seen in cases of alimentary allergy. They feel, too, that adequate vitamin C in the diet does not decrease the sensitivity of the subject to a substance but prevents hyperemia of the digestive tract and consequently decrease in absorption of the unchanged protein. Increased absorption may occur also with other types of injury to the digestive tract or other nutritional deficiency, such as a lack of vitamin A in the diet. HOYER, Cincinnati.

EFFECT OF POLLEN CONTACT UPON THE AGE OF ONSET OF HAY FEVER. J. ALEXANDER CLARKE JR. and HOWARD C. LEOPOLD, J. Allergy **11**:496 (July) 1940.

The authors present a comparison of two groups of sufferers from hay fever, one made up of persons born in America and the second made up of persons born in Europe. All spent their American years near Philadelphia.

Exposure to the pollen is the important factor. The European sufferers required the same "incubation period" after the first contact with pollen as did the American patients, regardless of their age at the time of contact.

The concentration of the exposure is a factor, as was evidenced by the predominance of boys in the first decade of life.

Exposure to substances other than pollen, such as orris root, dust, etc., may account for the results of treatment, especially in women. HOYER, Cincinnati.

LIPODYSTROPHIA FACIALIS. RUBIN GURALNICK and HYMAN GREEN, New England J. Med. **220**:553 (March 30) 1939.

In reporting 6 cases of lipodystrophy, Parmelee states that the disease affects children chiefly between the ages of 5 and 8 years, the ratio of girls to boys being 2:1. The chief characteristics in his 6 cases were a thin, cadaverous facies and emaciation of the upper part of the trunk, the rest of the body appearing either normal or better than normal. There was no assignable cause for the malady in any of his patients, and the general health of all was very good.

The condition is apparently the same as Simon's disease but is to be differentiated from Simmond's disease (facioscapulohumeral muscular dystrophy; progressive muscular atrophy; progeria; malnutrition; cachexia).

GENGENBACH, Denver.

RELATION OF PANTOTHENIC ACID TO DERMATITIS OF THE RAT. L. R. RICHARDSON and A. G. HOGAN, Proc. Soc. Exper. Biol. & Med. **44**:583 (June) 1940.

Rats had a mild dermatitis during administration of a ration of casein, sucrose, cellulose, cod liver oil salts, thiamine and riboflavin. All the animals in one group of rats given vitamin B_6 improved but there was a recurrence of the dermatitis within fifteen days in 9 of 11 animals. Of 10 rats given pantothenic acid, 2 were cured and some improved. When both vitamin B_6 and pantothenic acid were given the animals recovered within a week and made considerable gains in weight. Three animals which failed to respond to vitamin B_6 therapy and were at the point of death responded favorably when pantothenic acid was administered.

HANSEN, Minneapolis.

NEUROFIBROMATOSIS OF RECKLINGHAUSEN IN CHILDREN AND ITS RELATION TO PLEXIFORM NEUROMA. C. TORRICELLI, Pediatria **47**:891 (Oct.) 1939.

The author reviews the principal theories concerning the etiology and histogenesis of peripheral nerve tumors and the neurofibromatosis of Recklinghausen. The case of a 13 year old boy with peripheral nerve tumors and a plexiform neuroma of the tongue is presented. The tumor of the tongue was first noted at the age of 3 years, and it gradually increased in size. At birth there was noted a spot 4 cm. in diameter, of a coffee and milk color. The histologic appearance of the tumor of the tongue and of a peripheral tumor is reported. The author concludes that the plexiform neuroma is a part of the same syndrome, and he thinks that the most probable theory as to cause is that of a "neuroectomesodermatosis."

MARTOCCIO, Utica, N. Y.

ALLERGIC DISEASES IN INFANCY; BRIEF HISTORICAL FACTS—ORGANIZATION—ORIENTATION—OBSERVATIONS. CAUPOLICÁN R. CASTILLA, Rev. méd. latinoam. **25**:171 (Nov.) 1939.

This study of asthmatic children was begun twenty years ago. It was broadened and organized during the next ten years to include clinical observations, laboratory data and various tests. Finally, in June 1935, it was officially organized into "the first study, investigation and treatment of the allergic diseases of

infancy" in the Argentine Republic. This clinical service is located in the Children's Hospital at Buenos Aires, under the auspices of the Society of Beneficence.

Because of the frequency in infancy of asthma, eczema, urticaria and rhinitis, emphasis is given to the study and treatment of these diseases. Asthma occupies first place.

This special service makes a complete study of the disease; a minutely detailed history of the patient, to which great importance is attached, is taken; an analysis of urine, Wassermann, Kahn and Mantoux tests, an analysis of blood (eosinophilia, erythrocyte sedimentation), an electrocardiogram, etc., are made. Roentgenograms at different stages of the disease are also taken.

To investigate the reactions of allergy, tests with different strengths are used, according to the age of the child and the need of each patient. These tests are repeated if necessary, intradermally or by scratch.

This department has at its disposal all the modern means of research required by this branch of medicine and has the cooperation of the personnel of the hospital, the laboratories and the consultation offices.

The orientation of this special department is entirely clinical, and the allergic child is a patient of the medical clinic. Consequently, the study made of him according to the organic-functional concept is as complete as possible. The laboratory examinations and the allergic tests are made with the object of treating each patient individually.

The treatment, described in earlier publications by the author or by his associates, is based on a general, special or specific desensitization; the general basic treatment and the organic-functional condition of the patient are also considered.

In this article the author describes detailed studies of allergic patients; he discusses the making of roentgenograms of the asthmatic patient, eosinophilia, blood calcium, tuberculosis, syphilis, heredity, cutaneous tests, the most common sensitizing agents in Buenos Aires, the climate, the effect of certain meteorologic conditions, etc.

The detailed clinical histories compiled during fifteen, ten or five years of care are at the disposal of persons interested in this study.

DWYER, Kansas City, Mo.

INVESTIGATIONS OF THE SENSIBILITY OF THE SKIN TO BEE VENOM IN ALLERGIC DISEASES (A CONTRIBUTION TO THE CLINICAL MEASUREMENT OF THE DYNAMIC FEATURES OF ALLERGIC PHENOMENA). E. TRAUB, Acta pædiat. **27**:177, 1939.

Theoretic considerations suggest that bee venom is a suitable reagent for the investigation of parallergic phenomena. Accordingly, studies were undertaken in which this substance was employed for the purpose of distinguishing between the specific reactivity of the skin to true allergens and its nonspecific parallergic reactive capacity. Exaggerated nonspecific reactivity was demonstrated in cases of asthma. An attempt was made to employ this datum in the diagnosis of ambiguous asthmatic states; its possible therapeutic use is discussed. Studies were made of acute rheumatic infection. In cases of tuberculosis the intensity of the reaction was found to parallel the degree of tuberculin sensitivity; on the contrary, a conspicuous diminution of cutaneous sensitivity to the venom was found to characterize lobar pneumonia. Accordingly, efforts were directed to working out a test that would distinguish between tuberculous and nontuberculous pulmonary consolidation. Cutaneous reactivity was found to be suppressed in the presence of early scarlet fever; the inoculation of the venom produced blanching resembling that of the Schultz-Charlton phenomenon. The reaction appeared to be intensified in the presence of catarrhal jaundice. These discoveries are interpreted to signify that bee venom is more than a simple irritant; on the contrary, by virtue of its content of histamine and other substances it bears an affinity to the chemical aspects of antigen-antibody reactions.

Miscellaneous

EFFECT OF ULTRAVIOLET RADIATION ON ROENTGEN RAYS: DO ULTRAVIOLET RAYS HAVE A DELETERIOUS EFFECT ON ROENTGEN RAYS WHEN APPLIED TO THE SKIN? FRANCIS A. ELLIS and HAYDEN KIRBY-SMITH, Arch. Dermat. & Syph. **42**:466 (Sept.) 1940.

It is the opinion of the authors that the former lack of adequate accurate measurements of dosage, mistakes in technic and overdosage, and not a concomitant actinic dermatitis or a dermatitis due to external irritants, are the main causes for roentgen ray sequelae.

The late cutaneous changes due to the combined application of roentgen rays and actinic rays are usually a summation of one plus the other, and the combined use of the two modes of therapy does not accentuate the effect of either agent.

For over two years the authors have used strong sulfur lotions in conjunction with accurately measured roentgen therapy in the treatment of acne, without any evidence of roentgen ray sequelae.

JACKSON, Iowa City.

SKIN, CONJUNCTIVAL AND SCLERAL REACTIONS IN THE COURSE OF THERAPY WITH SULFATHIAZOLE. JAMES W. HAVILAND and PERRIN H. LONG, Bull. Johns Hopkins Hosp. **66**:313 (May) 1940.

Ten cases of cutaneous eruptions and 6 cases of conjunctival reactions in a group of 78 patients treated with sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) are reported. So far as we have been able to determine, the conjunctival injection constitutes an entirely new type of reaction to sulfanilamide and its derivatives. The relation of these reactions to exposure to light is discussed.

AUTHORS' SUMMARY.

EFFECT OF SULFAPYRIDINE ON PHAGOCYTOSIS AND DISSOCIATION. R. TUNNICLIFF, J. Infect. Dis. **66**:148 (March-April) 1940.

"Sulfapyridine diluted 1:1,000 to 1:100,000 in salt solution promotes phagocytosis of greening streptococci, staphylococci and non-encapsulated pneumococci. It stimulates the activity of leukocytes if serum is present, but does not act as opsonin.

"Streptococci and pneumococci grown in 1:1000 sulfapyridine plain broth show by chain formation and staphylococci by slight colony change some S-R dissociation which makes the organisms more phagocytable than an equal number in the S phase. Pneumococci grown in 1:1000 sulfapyridine dextrose broth are not more phagocytable except after several transfers in sulfapyridine dextrose broth, probably on account of the presence of fewer capsules.

"One cc. of a 1:1000 sulfapyridine solution injected subcutaneously into mice prevents abscess formation by staphylococci injected intraperitoneally. If staphylococci are mixed with mucin, more severe reactions take place but the results are similar.

"Smear preparations from the peritoneal cavity of mice injected with staphylococci with and without sulfapyridine indicate that beginning one hour after receiving sulfapyridine, staphylococci are removed from the peritoneal cavity by phagocytosis."

AUTHOR'S SUMMARY.

INTRAMUSCULAR ADMINISTRATION OF SODIUM SULFAPYRIDINE. LYNN HALL, EDWARD THOMPSON and RAYMOND WYRENS, J. Lab. & Clin. Med. **26**:314 (Nov.) 1940.

A 33.3 per cent solution of sodium sulfapyridine in sterile water was used for intramuscular injection in 25 cases. The blood levels and results were comparable to those obtained with oral administration. There was no evidence of local irritation.

GARD, Galveston, Texas.

QUININE POISONING: REPORT OF A FATAL CASE. P. P. LYNCH and C. W. BRANDT, New Zealand M. J. **39**:191 (Aug.) 1940.

A brief review of the literature is presented, as well as a case report. A child 20 months of age ingested between 50 and 100 grains (3 and 6 Gm.) of quinine, which resulted in death. Quinine apparently is very rapidly absorbed from the small intestine and may account for early death.

WEIGAND, Indianapolis.

CONTINUOUS HYPODERMOCLYSIS. RIBADEAU-DUMAS, DUFOUR and GRU-UMBACH, Bull. Soc. pédiat. de Paris **37**:205 (April) 1939.

Eleven infants were given hypodermoclysis in the thighs by the drip method in order to combat dehydration. The results were considered fairly good. In 4 cases subcutaneous abscesses developed. These may be avoided, the authors presume, by the observance of strictly aseptic technic and careful adjustment of the rate of flow of the drip. They used isotonic solutions of dextrose and of sodium bicarbonate and Ringer's solution, and injected as much as 960 cc. in twenty-four hours. They recommend 150 Gm. per kilogram of body weight. The thighs are alternated after fifteen to twenty-four hours of infiltration.

BENJAMIN, Montreal, Canada.

TERATOID GROWTH ON CHILD'S HEAD. LUDWIG RATHCKE, Beitr. z. klin. Chir. **168**:610, 1938.

A large teratoid tumor on the head of a 3 week old infant is described. This is an unusual location for such a growth.

The tumor was removed, with excellent results.

RUBIN, Boston.

TISSUE PHOSPHATASE IN LEAD POISONING. T. YAGIHARA, Acta pædiat. japon. **46**:944 (Aug.) 1940.

The author examined the glycerol phosphatase content of various tissues by the method of Izumi-Takamatsu and reports that the greatest increase occurred in the liver and kidney, while the intestinal mucosa, muscles, myocardium and brain showed practically no increase. A slight increase in this enzyme was noted at the ends of the long bones, corresponding to the locations of the so-called lead line.

KATO, Chicago.

THE OXYGEN CARBON-DIOXIDE MIXER, TYPE K. L. V.: A NEW APPARATUS FOR OXYGEN THERAPY. A. LICHTENSTEIN and E. MANNHEIMER, Acta pædiat. **27**:168, 1939.

A closed system is described which permits the controlled enrichment of atmospheric air with oxygen from a storage cylinder and with carbon dioxide from the patient's own expired gases. Admission of the oxygen under the pressure of the storage tank provides for circulation; expansion of the gas keeps the system cooled to room temperature. Moisture is absorbed to the degree desired by passing the air through a siliceous gel. An automatic alarm indicates cessation of circulation or exhaustion of the oxygen supply. The rate of consumption of oxygen is only 1,500 cc. per minute.

MCCUNE, New York.

Book Reviews

Health and Longevity. By Charles M. Baird. Price, $1.75. Pp. 157, with 14 tables. Boston: The Christopher Publishing House, 1941.

This book, apparently written for the laity, is given an appearance of authenticity by a foreword embodying a statement by C. V. Akin, Assistant Surgeon General of the United States Public Health Service, and a concluding paragraph quoted from an issue of *The Journal of the American Medical Association.* When so much good work is being done in the field of health education of the public, it is unfortunate that books such as this are published.

Charles M. Baird is not known to the reviewer, but he is evidently not a physician, and the book gives no evidence that he has had scientific training.

In the early pages he suggests that periodic examinations by or consultations with one's own physician are of value. There are many statements in the book with which his own physician would not agree. To quote but a few: "Impaired eye sight is almost always caused by weakened eye muscles." "Dandruff in nine cases out of ten causes baldness." "Vacuum cupping of the scalp will grow hair." "Smallpox, infantile paralysis, meningitis and twenty-three other infectious diseases begin with the common cold." "Diphtheria is due to the lack of vitamins A, B, D, calcium and iodine; coryza, toxicosis."

The chapter on nutrition is marked by the food faddist's belief that the ingestion of protein and carbohydrate at the same meal is dangerous.

In the discussion of the etiologic factors of disease he shows his ignorance of the role bacteria play. He occasionally advises the use of proprietary remedies for common ailments.

The book on the whole is a mass of semiscientific jargon; it embodies many of the notions advanced by health and food faddists and contains little that is sound.

The Endocrine Function of Iodine. By William Thomas Salter. Price, $3.50. Pp. 350, with 45 tables and 40 illustrations. Cambridge: Harvard University Press, 1940.

While this volume is not intended primarily as a clinical treatise, the clinician, as well as the biochemist and the physiologist, will find it interesting and useful. Although it deals chiefly with iodine in relation to the endocrine glands, as the table of contents indicates, it includes many data concerning other features of iodine metabolism.

The material is arranged as follows: (1) iodine balance and endocrine balance, (2) iodine stores in body tissues, (3) iodine compounds of biologic importance, (4) circulating iodine, (5) thyroid activity, (6) endocrine balance, (7) iodine and the pituitary-ovarian axis, (8) neurologic influence of iodine, (9) iodine balance, (10) radioactive iodine and (11) clinical problems. Following these are a section on chemical methods—called an appendix for laboratory workers—a bibliography and a subject index.

Throughout the book the author carefully distinguishes between established fact and ideas which will require much more study and added data before they can be substantiated to the satisfaction of the "iatrochemist," by which term the author refers to himself.

This book can be recommended as a valuable addition to the libraries of workers engaged in the investigation of chemical problems concerning iodine and the endocrine glands, particularly the thyroid gland, and of the clinician who is interested in something more than a merely didactic approach to the clinical problems which involve the thyroid gland and its relation to iodine metabolism.

Psychologie des Neugeborenen Kindes. By F. Stirnimann. Price, 3.5 francs. Pp. 108, with no illustrations. Zurich: Rascher & Cie., 1940.

This small volume relates the author's extensive observations on several hundred newborn infants. Unlike Gesell, Pratt and Feldman, who reckon the newborn period as being the first month of life, Dr. Stirnimann considers it to comprise about the first fourteen days and also believes that it is not of uniform length for all babies but is a function, or consequence, of certain conditions within the child. Dr. Stirnimann would substitute for "reflex" or "reaction" the Anglo-American term "response" as being more accurate to describe the behavior of the newborn infant. The book contains a clear exposition of the author's experimental procedure in investigating the senses of touch, pressure, warmth, cold, pain, taste, smell, hearing, seeing and balance, as well as feeling, memory and impulses. One interesting discovery in regard to the sense of touch is that infants do not respond so readily to inanimate material, such as a wooden stick or a brush, as they do to living matter, such as one's finger.

Although Dr. Stirnimann does not neglect the neurologic explanation of his results, the major contribution of the book, it seems to the reviewer, is the psychologic interpretation of his observations. While he occasionally goes beyond the experimental evidence in his theoretic discussion, he displays a keen understanding of the manifestations of mental development of the newborn child, and his book should be of particular value to those interested in the intellectual development of young infants. It is easy to read, it presents practical ideas for the construction and administration of mental tests and it raises challenging questions about infant behavior for which there are as yet no answers.

Bacteriology in Neuropsychiatry. By Nicholas Kopeloff, Ph.D. Price, $4.50. Pp. 316, with no illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1941.

The effects of micro-organisms on the central nervous system are protean. The author of this book presents the contributions which bacteriology and immunology have made to neurology.

Part 1 deals with the diseases of known etiology in which there is primary involvement of the nervous system; they include meningitis, encephalitis, herpes zoster, rabies and poliomyelitis. Part 2 is concerned with diseases of known etiology in which there is secondary involvement of the nervous system, such as abscess of the brain, tuberculosis, leprosy, typhus, diseases caused by viruses and protozoa, tetanus, diphtheria, botulism and dysentery. Part 3 summarizes the information available on the diseases of unknown etiology in which there is involvement of the nervous system (functional psychoses, for example), the importance of toxins in schizophrenia and the role of bacterial agents in epilepsy, chorea and encephalitis. Part 4 is a consideration of the immunologic aspects of the central nervous system.

Parts 1 and 2 are devoted to established bacteriologic principles. Parts 3 and 4 give the evidence on which the theories about the effect of bacterial agents on the nervous system are based. This authoritative book will be interesting to any physician, both as a reference book and as a review, and it will serve as a good summary of present day knowledge regarding many controversial subjects; for instance, the role of infection in the functional disorders.

Feeding Our Old Fashioned Children. By Dr. C. Anderson Aldrich and Mary M. Aldrich. Price, $1.75. Pp. 112, with 6 illustrations. New York: The Macmillan Company, 1941.

"Feeding Our Old Fashioned Children" has much more to offer than might be inferred from the title. Dr. and Mrs. Aldrich show how mental and emotional

growth may be affected favorably or adversely by the relationships established at feeding time. If eating becomes a problem, nutrition, as well, may be impaired.

The first chapters cover the physiology of hunger and appetite and stress individual rhythm as a factor in the obtaining of satisfaction at mealtime. They also deal with beginning illnesses and emotional upsets as causes of the child's refusal of food.

Other chapters show how by understanding and encouraging the child's efforts to manage his own environment, one may make mealtime a source of satisfaction in accomplishment and so contribute to his self reliance and social adaptability. The discussion indicates how the effects of a bad start in handling the child's feeding may be remedied by substituting an intelligent response to his needs for the imposition of arbitrary authority.

The book may be recommended unreservedly. It should serve as a useful and interesting guide even to those mothers whose children apparently present no feeding problems. The excellent photographic illustrations are by Frank Selfridge.

Plague on Us. By Geddes Smith. Price, $3.00. Pp. 365, with 24 illustrations. New York: The Commonwealth Fund, 1941.

Recently there has been a great deal of medical writing for lay readers. Much of it has been of questionable worth, but this evaluation does not apply to "Plague on Us."

This book, written by an authority, considers the question of epidemics from many standpoints. It is written for the layman, but the author, while keeping his audience in mind, has not made the fatal error of giving the subject too simple an interpretation. Many of the points which he brings out are not so well known by physicians but that they could derive much benefit from reading about them. On the whole, the book is an admirable example of medical interpretation to the layman and is to be recommended to any reader, whether layman or physician, who wants a well authenticated and clear exposition of the subject.

It will not be especially encouraging to the reader to learn that there is little hope of combating another epidemic of influenza any more successfully than was that of 1918, but it is true and one must face the facts. Also, one should not be too sure that many of the diseases which are apparently on the way out will not stage a revival, as the author so conservatively points out. This is a good book and a safe one.

How to Raise a Healthy Baby. By Dr. L. J. Halpern. Price, $1.95. Pp. 388, with 29 illustrations. New York: Prentice-Hall, Inc., 1940.

In this book, which is written in a pleasing style, the author through questions and answers has covered the everyday problems of the child in health and disease. Special emphasis has been placed on diet, growth and development and care and training from birth to the age 6 years. The book gives no medical advice which might lead to "home prescribing." Instead, it emphasizes the importance of periodic visits to the physician's office and early consultation with him whenever the child shows any departure from normal health.

There may be differences of opinion about some of the advice given, but these differences will prove no greater than the divergences in ideas about methods of daily practice which are common among physicians.

Throughout the book the author has attempted to explain simply and sanely to the uninformed mother the mental and physical requirements of the growing child. This is a book which physicians interested in the proper guidance of children might safely recommend to mothers.

Manual of Applied Nutrition: Diets Compiled by the Dietary Department of the Johns Hopkins Hospital. Price, $1.00. Pp. 86, with no illustrations. Baltimore: Johns Hopkins Press, 1941.

The material in this manual has been prepared through the collaboration of a special committee on nutrition and the dietary department of the Johns Hopkins Hospital. It has been approved by members of the staff representing all services. It is designed primarily for the use of the visiting and house staffs, nurses, dietitians and medical students and gives in detail the composition of the different types of diets in use, so that one may know, for example, just what the patient gets when a full diet, a soft diet or a diet for a patient with cardiac disease is ordered. The deficiencies of certain diets are pointed out so that they may not be used over too long a period or that additions of vitamins and minerals may be made.

The material is conveniently arranged, with one type of diet to a page. Supplementary data, such as height-weight charts and normal values for the chemical constituents of the blood, are appended.

Doctrina y practice de la profilaxis de la tuberculosis. By Dr. Louis Saye. Price, none given. Pp. 355, with 170 illustrations. Buenos Aires: Editorial Sudamericana, 1940.

The author presents the results of studies and an analysis of experiments in the epidemiology and prophylaxis of tuberculosis which indicate careful observation of clinical cases. In each case the racial, social and economic conditions were analogous. Many controls were used. Dr. Saye has utilized the services of physicians in Chile, Argentina, Peru and Uruguay for the purpose of obtaining authentic local information. With the help of the data obtained from these investigators, he compares conditions in Montevideo with those in other countries in South America which have similar problems. The conclusions reached are conservative and indicate a rational scientific approach to the problems discussed.

The Merck Index. Seventh edition. Price, in the United States, $2; elsewhere, $2.50. Pp. 1462, with no illustrations. Rahway, N. J.: Merck & Co., Inc., 1940.

Merck & Co., Inc., has again provided a complete manual of therapeutics and materia medica. Thirteen hundred and twenty pages are devoted to various illnesses, arranged in alphabetical order and discussed briefly from the point of view of etiology, diagnosis, therapy, prophylaxis and treatment. This section is followed by a table of doses in which the drugs are arranged alphabetically. There is a presentation of facts about the preparations distributed by Merck & Co., Inc., and miscellaneous tables complete the book. This manual should prove exceedingly handy as a reference book for any physician.

Health, Mental, Moral and Physical. By Dr. Horace W. Soper. Price, $1.50. Pp. 109, with no illustrations. Boston: The Christopher Publishing House, 1941.

This book is composed of a series of delightful essays, many of which are reminiscent. Some deal primarily with subjects specifically relating to the health of the individual and of society, and others are biographic. All give evidence of the author's keen observation, good judgment, wide reading of classical, as well as medical, literature and underlying kindliness and humor.

News and Comment

GENERAL NEWS

Residencies in Pediatrics.—Residencies in the specialty of pediatrics are available to qualified medical graduates at the Los Angeles County Hospital, and will be filled from an eligible list to be established on the basis of an unassembled, open competitive civil service examination, according to an announcement just made by the Los Angeles County Civil Service Commission. Applications to take the examination must be filed with the commission by Friday, July 18. The usual three year Los Angeles County residence requirement has been waived.

Candidates must have been graduated with the degree of doctor of medicine from an approved medical school within six years prior to Jan. 1, 1941 and must have completed an internship of at least one year in an approved hospital. A residency, second year of internship or postgraduate work in an approved medical school giving graduate instruction is desirable.

The length of service is two years; an additional year's service in the communicable disease unit of the hospital may be granted at the discretion of the director. Uniforms and medical care will be provided; in addition, $50 a month will be paid for the first year and $115 a month for the second and the third year (if additional year is granted).

Application blanks and additional information concerning the examination may be obtained from the office of the Los Angeles County Civil Service Commission, room 102, County Hall of Records, Los Angeles.

Pan-American Congress on Child Hygiene.—The eighth Pan-American Congress on Child Hygiene will be held in Washington, D. C., March 28 to April 4, 1942.

SOCIETY NEWS

American Pediatric Society.—At the recent meeting of the American Pediatric Society the following officers were elected: president, Dr. Edwards A. Park; vice president, Dr. Joseph B. Bilderback; secretary-treasurer, Dr. Hugh McCulloch; recorder-editor, Dr. Heyworth N. Sanford, and member of the council, Dr. Allan M. Butler.

The following physicians were elected to active membership: Dr. Waldo E. Nelson, Philadelphia; Dr. John A. V. Davies, Boston; Dr. Lee E. Farr, Wilmington, Del.; Dr. Harry H. Gordon, New York; Dr. Horace L. Hoves, Baltimore; Dr. Laslo Kajdi, Baltimore; Dr. R. R. Struthers, Montreal, Canada; Dr. Henry G. Poncher, Chicago; Dr. Bruce Chown, Winnipeg, Manitoba, Canada; Dr. Joseph Warkany, Cincinnati, and Dr. Stanley Gibson, Chicago.

Society for Pediatric Research.—Dr. George M. Guest, of Cincinnati, was recently elected president of the Society for Pediatric Research.

DEATHS

Dr. Paul B. Bender, of Philadelphia, chief pediatrician at the Kensington Hospital for Women, died May 13, at the age of 54.

Directory of Pediatric Societies*

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

International Congress of Pediatrics

President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
General Secretary: Dr. Kenneth D. Blackfan, 300 Longwood Ave., Boston.
Assistant Secretary-Treasurer: Dr. Charles F. McKhann, University of Michigan, Ann Arbor, Mich.

Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. H. P. Wright, 1509 Sherbrooke St. W., Montreal.
Place: Boston. Time: Postponed indefinitely.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

British Paediatric Association

President: Prof. Charles McNeil, 44 Heriot Row, Edinburgh, Scotland.
Secretary: Dr. Arthur G. Maitland Jones, 31A Weymouth St., London, W. 1.

Danish Pediatric Society

President: Dr. E. Lenstrup, Copenhagen.
Secretary: Dr. E. Gjørup, Dronning Louises Børnehospital, Copenhagen.

Nederlandsche Vereeniging voor Kindergeneeskunde

President: Prof. Dr. J. van Lookeren Campagne, Hofstraat 16, Gröningen, Holland.
Secretary: Dr. R. P. van de Kasteele, Laan van Poot 340, 's Gravenhage, Holland.
Place: Different places. Time: Three times a year.

Paediatrický Spolok na Slovensku

President: Dr. A. J. C. Chura, Lazaretská 11, Bratislava.
Secretary: Dr. P. Rados, Lazaretská 6, Bratislava.
Place: Pediatric Clinic, University Bratislava. Time: Six times a year.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

ROYAL SOCIETY OF MEDICINE, SECTION FOR THE STUDY OF DISEASE IN CHILDREN

President: Dr. E. A. Cockayne, 98 Harley St., London, W. 1, England.
Secretary: Dr. R. Lightwood, 86 Brook St., London, W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p. m.

PALESTINE JEWISH MEDICAL ASSOCIATION, SECTION OF PHYSICIANS OF CHILDREN'S DISEASES

President: Prof. S. Rosenbaum, 26 Bialikstr., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

SOCIEDAD CUBANA DE PEDIATRÍA

President: Dr. Clemente Inclan Costa, Manrique 48, Habana.
Secretary: Dr. Serafin Falcon Lopez, Calle B No. 356, Vedado, Habana.
Place: Cátedra de Clinica Infantil, Hospital Mercedes, Habana. Time: Last Wednesday of every month.

SOCIEDAD MEXICANA DE PEDIATRIA

President: Dr. Jorge Muñoz Turnbull, Av. Alvaro Obregón 186, Mexico, D. F.
Secretary: Dr. Fernando López Clares, Medellín 191, Mexico, D. F.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Dr. B. Weill-Hallé, 49 Avenue Raymond Poincaré, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue du Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Malades, 49 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

URUGUAYAN SOCIETY OF PEDIATRICS

President: Dr. Conrado Pelfort, Av. 18 de Julio 1246, Montevideo.
Secretary: Dr. Héctor Mourigan, Av. 18 de Julio 2175, Montevideo.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON PEDIATRICS

Chairman: Dr. Philip M. Stimson, 25 Claremont Ave., New York.
Secretary: Dr. Hugh L. Dwyer, 315 Alameda Rd., Kansas City, Mo.
Place: Atlantic City.

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. Richard M. Smith, 66 Commonwealth Ave., Boston.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Place: Statler Hotel, Boston. Time: Oct. 9-11, 1941.
Region I. Place: Philadelphia.

AMERICAN HOSPITAL ASSOCIATION, CHILDREN'S HOSPITAL SECTION

Chairman: Dr. D. L. Richardson, 593 Eddy St., Providence, R. I.
Secretary: Dr. Joelle C. Hiebert, 299 Main St., Lewiston, Maine.

AMERICAN PEDIATRIC SOCIETY

President: Dr. Edwards A. Park, Johns Hopkins Hospital, Baltimore, Md.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid Ave., St. Louis.

CANADIAN SOCIETY FOR THE STUDY OF DISEASES OF CHILDREN

President: Dr. L. M. Lindsay, 815 Medical Arts Bldg., Montreal.
Secretary-Treasurer: Dr. Elizabeth Chant Robertson, Hospital for Sick Children, Toronto.
Place: Brockville, Ontario. Time: June 14, 1941.

SOCIETY FOR PEDIATRIC RESEARCH

President: Dr. George M. Guest, Children's Hospital, Cincinnati.
Secretary: Dr. Mitchell I. Rubin, 1740 Bainbridge St., Philadelphia.

SECTIONAL

INTERMOUNTAIN PEDIATRIC SOCIETY

President: Dr. Eugene Smith, 385–24th St., Ogden, Utah.
Secretary-Treasurer: Dr. W. C. Cheney, 837 Boston Bldg., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

NEW ENGLAND PEDIATRIC SOCIETY

President: Dr. R. Cannon Eley, 319 Longwood Ave., Boston.
Secretary-Treasurer: Dr. James Marvin Baty, 319 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

NORTH PACIFIC PEDIATRIC SOCIETY

President: Dr. S. G. Henricke, 4215 N. E. Hancock St., Portland, Ore.
Secretary: Dr. J. S. Backstrand, 333 Wyatt Court, Salem, Ore.
Place: Vancouver, B. C. Time: June 21, 1941.

ROCKY MOUNTAIN PEDIATRIC SOCIETY

President: Dr. Donn Barber, 802½–8th Ave., Greeley, Colo.
Secretary: Dr. Kenneth Schmidt, Republic Bldg., Denver.
Place: Children's Hospital, Denver. Time: First Saturday of each month from September to May, inclusive, 7:30 p. m.

SOUTHERN MEDICAL ASSOCIATION, SECTION OF PEDIATRICS

Chairman: Dr. Harvey F. Garrison, 319 E. Capitol St., Jackson, Miss.
Secretary: Dr. Warren W. Quillian, 227 Aragon Ave., Coral Gables, Fla.

STATE

ALABAMA PEDIATRIC SOCIETY

President: Dr. M. V. Adams, 803 Government St., Mobile.
Secretary-Treasurer: Dr. William R. Britton, 4 Catoma St., Montgomery.

ARKANSAS STATE PEDIATRIC ASSOCIATION

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

CALIFORNIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. William Belford, 233 A St., San Diego.
Secretary: Dr. John J. Miller Jr., 2398 Sacramento St., San Francisco.

FLORIDA STATE PEDIATRIC SOCIETY

President: Dr. Warren W. Quillian, 227 Aragon Ave., Coral Gables.
Secretary: Dr. George N. Leonard, 605 Lincoln Rd., Miami Beach.
Place: Concurrent with state association meeting at time of convention.

GEORGIA PEDIATRIC SOCIETY

President: Dr. R. C. McGahee, 1345 Greene St., Augusta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.

HEZEKIAH BEARDSLEY PEDIATRIC CLUB OF CONNECTICUT

President: Dr. D. C. Darrow, 789 Howard Ave., New Haven.
Secretary: Dr. Joseph L. Hetzel, 103 N. Main St., Waterbury.
Time: Three meetings a year.

ILLINOIS STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. Orville Barbour, 331 Fulton St., Peoria.
Secretary: Dr. Craig Butler, 715 Lake St., Oak Park.

INDIANA STATE PEDIATRIC SOCIETY

President: Dr. K. T. Knode, 1105 E. Jefferson Blvd., South Bend.
Secretary-Treasurer: Dr. Mathew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

IOWA PEDIATRIC SOCIETY

President: Dr. Morgan J. Foster, 837 Higley Bldg., Cedar Rapids.
Secretary-Treasurer: Dr. Arnold M. Smythe, 406–6th Ave., Des Moines.

LOUISIANA STATE PEDIATRIC SOCIETY

President: Dr. Julian Graubarth, 3431 Prytania St., New Orleans.
Secretary-Treasurer: Dr. W. C. Rivenbark, 3503 Prytania St., New Orleans.

MEDICAL SOCIETY OF STATE OF NEW YORK, SECTION ON PEDIATRICS

Chairman: Dr. Norman L. Hawkins, 11 Public Sq., Watertown, N. Y.
Secretary: Dr. William J. Orr, 135 Linwood Ave., Buffalo.

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA, PEDIATRIC SECTION

Chairman: Dr. John D. Sturgeon Jr., 22 N. Gallatin Ave., Uniontown.
Secretary: Dr. Elwood W. Stitzel, 403 Central Trust Bldg., Altoona, Pa.
Place: Pittsburgh. Time: Sept. 29-Oct. 2, 1941.

MICHIGAN STATE MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. Harry Towsley, University of Michigan Hospital, Ann Arbor.
Secretary: Dr. Leon DeVel, 110 E. Fulton, Grand Rapids.

MISSISSIPPI STATE PEDIATRIC SOCIETY

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

NEBRASKA PEDIATRIC SOCIETY

President: Dr. J. C. Iwersen, 236 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. Elmer W. Bantin, 440 Aquila Court Bldg., Omaha.
Place: As announced by Committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

NEW HAMPSHIRE PEDIATRIC SOCIETY

President: Dr. MacLean J. Gill, 14 N. State St., Concord.
Secretary-Treasurer: Dr. Ursula G. Sanders, 46 Pleasant St., Concord.
Time: Twice yearly.

NORTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Thomas M. Watson, Greenville.
Secretary: Dr. Frederick B. Haar, Greenville.

OKLAHOMA STATE PEDIATRIC SOCIETY

President: Dr. Ben H. Nicholson, 301 N.W. 12th St., Oklahoma City.
Secretary: Dr. Luvern Hays, 108 W. 6th St., Tulsa.
Place: Oklahoma Club. **Time:** 6:30 p. m., fourth Friday of each alternate month from September to May, inclusive.

SOUTH CAROLINA PEDIATRIC SOCIETY

President: Dr. R. B. Josey, 1517 Hampton Ave., Columbia.
Secretary-Treasurer: Dr. Wilson Ball, South Carolina State Health Dept., Columbia.

TENNESSEE STATE PEDIATRIC SOCIETY

President: Dr. Kinsey M. Buck, 1193 Madison Ave., Memphis.
Secretary: Dr. Gilbert Eblen, 611 W. Main Ave., Knoxville.

TEXAS PEDIATRIC SOCIETY

President: Dr. P. E. Luecke, 4105 Live Oak St., Dallas.
Secretary-Treasurer: Dr. John Ashby, 3610 Fairmount Ave., Dallas.

VIRGINIA PEDIATRIC SOCIETY

President: Dr. John M. Bishop, 511 Medical Arts Bldg., Roanoke.
Secretary: Dr. Edwin A. Harper, 301 Rivermont Ave., Lynchburg.

WEST VIRGINIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

President: Dr. Theresa O. Snaith, 450 Center Ave., Weston.
Secretary: Dr. Henrietta L. Marquis, 211 Bair Bldg., Beckley.

LOCAL

ACADEMY OF MEDICINE OF CLEVELAND, PEDIATRIC SECTION

Chairman: Dr. J. D. Nourse, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. I. B. Silber, 10465 Carnegie Ave., Cleveland.
Place: Cleveland Medical Library Bldg. Time: October, December, February and April.

ACADEMY OF MEDICINE, TORONTO, SECTION OF PEDIATRICS

President: Dr. I. Nelles Silverthorne, 170 St. George St., Toronto, Canada.
Secretary: Dr. G. P. Hamblin, 2333 Bloor St. W., Toronto, Canada.

BRONX PEDIATRIC SOCIETY

President: Dr. David Greene, 910 Grand Concourse, New York.
Secretary: Dr. F. E. Chick, 2325 University Ave., New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Every second Wednesday of each month, except June, July, August and September.

BROOKLYN ACADEMY OF PEDIATRICS

President: Dr. John A. Monfort, 861 Carroll St., Brooklyn.
Secretary: Dr. Walter Coles, 604–2d St., Brooklyn.
Place: Kings County Medical Society Bldg. Time: Fourth Wednesday of each month, except May, June, August and September.

CENTRAL NEW YORK PEDIATRIC CLUB

President: Dr. Frank van der Bogert, 111 Union St., Schenectady.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Places: Various cities in New York. Time: Third Tuesday of April and September.

CHICAGO PEDIATRIC SOCIETY

President: Dr. Philip Rosenblum, 2376 E. 71st St., Chicago.
Secretary: Dr. A. L. Newcomb, 1791 W. Howard St., Chicago.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May, inclusive.

DALLAS PEDIATRIC SOCIETY

President: Dr. Edgar Loomis, 351 W. Jefferson Ave., Dallas, Texas.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmont Ave., Dallas, Texas.
Place: Bradford Baby Hospital. Time: 1 p. m., second and fourth Saturdays of each month.

DETROIT PEDIATRIC SOCIETY

President: Dr. Robert J. Mason, 460 Birmingham Rd., Birmingham, Mich.
Secretary: Dr. J. Hugh Lewis, 2966 Biddle Ave., Wyandotte, Mich.
Place: Wayne County Medical Society. Time: 8:30 p. m., first Wednesday of each month from October to June, inclusive.

FULTON COUNTY MEDICAL SOCIETY, PEDIATRIC SECTION (ATLANTA, GA.)

Chairman: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Secretary: Dr. Harry Lange, 478 Peachtree St. N. E., Atlanta.
Place: Academy of Medicine, 38 Prescott St. N. E. Time: Second Thursday of each month from October to April, 8 p. m.

HOUSTON PEDIATRIC SOCIETY

President: Dr. Thomas J. Donovan, 3820 Fannin St., Houston, Texas.
Secretary: Dr. Raymond Cohen, 2300 Caroline St., Houston, Texas.
Place: Houston Club. Time: Third Monday of each month.

KANSAS CITY (MISSOURI) PEDIATRIC SOCIETY

President: Dr. John Aull, 1103 Grand Ave., Kansas City.
Secretary: Dr. George Herrman, 1107 Bryant Bldg., Kansas City.
Place: Kansas City General Hospital. Time: On call.

LOS ANGELES COUNTY MEDICAL ASSOCIATION, PEDIATRIC SECTION

President: Dr. Alonzo Cass, 1908 Wilshire Blvd., Los Angeles.
Secretary-Treasurer: Dr. Gladys Patric Shahovitch, 3936 Roderick Rd., Los Angeles.
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Sydney Nussbaum, 247 Ocean View Ave., Brooklyn.
Secretary: Dr. Harry Bikoff, 850 St. Marks Ave., Brooklyn.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., second Monday of each month, October to March, inclusive.

Medical Society of the County of Queens, Inc., Section on Pediatrics

Chairman: Dr. A. A. Trivilino, 88-07–150th St., Jamaica, N. Y.
Secretary-Treasurer: Dr. Edith A. Mittell, 144–38th Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. Harry A. Ong, 1801 I St. N. W., Washington, D. C.
Secretary-Treasurer: Dr. William F. Burdick, 5402 Connecticut Ave. N. W., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: 8 p. m., fourth Thursday of every month.

Memphis Pediatric Society

President: Dr. E. C. Mitchell, 1073 Madison Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. Harry Jacobson, 1193 Madison Ave., Memphis, Tenn.
Place: John Gaston Hospital. Time: Quarterly.

Milwaukee Pediatric Society

President: Dr. R. P. Schowalter, 411 E. Mason St., Milwaukee.
Secretary-Treasurer: Dr. George H. Wegmann, 2650 W. Hopkins St., Milwaukee.
Place: Children's Hospital. Time: Second Wednesday of each alternate month, beginning with February.

New York Academy of Medicine, Section of Pediatrics

Chairman: Dr. Leslie O. Ashton, 850 Park Ave., New York.
Secretary: Dr. Alfred Langmann, 108 E. 68th St., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

Northern California Affiliates

President: Dr. Crawford Bost, 490 Post St., San Francisco.
Secretary: Dr. William A. Reilly, 384 Post St., San Francisco.
Time: Second Thursday of September, November, January, March and May.

Northwestern Pediatric Society

President: Dr. Harold Flanagan, 711 Lowry Medical Arts Bldg., St. Paul, Minn.
Secretary-Treasurer: Dr. George B. Logan, Mayo Clinic, Rochester, Minn.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

Oklahoma City Pediatric Society

President: Dr. J. Byron Snow, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. G. R. Felts, 1200 N. Walker St., Oklahoma City.
Place: Oklahoma Club. Time: Fourth Friday of each alternate month.

PHILADELPHIA PEDIATRIC SOCIETY

President: Dr. Philip S. Barba, 222 W. Harvey St., Germantown, Pa.
Secretary: Dr. Aims C. McGuinness, Children's Hospital, 1740 Bainbridge St., Philadelphia.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday of each month from October to April, inclusive.

PITTSBURGH PEDIATRIC SOCIETY

President: Dr. E. L. Piper, 3200–5th Ave., Pittsburgh.
Secretary-Treasurer: Dr. Carl Ruder, 646 Washington Rd., Mount Lebanon, Pittsburgh.
Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate month from October to June, inclusive.

RICHMOND PEDIATRIC SOCIETY

President: Dr. Louise Fry Galvin, 214 S. Boulevard, Richmond, Va.
Secretary-Treasurer: Dr. Herman W. Farber, 501 E. Franklin St., Richmond, Va.
Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: 8 p. m., third Thursday of each month, except June, July and August.

ROCHESTER PEDIATRIC SOCIETY

President: Dr. David Wolin, 16 N. Goodman St., Rochester, N. Y.
Secretary: Dr. W. L. Bradford, 16 N. Goodman St., Rochester, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee. Time: Third Friday of each month from October to May.

ST. LOUIS PEDIATRIC SOCIETY

President: Dr. Max Deutch, 634 N. Grand Blvd., St. Louis.
Secretary-Treasurer: Dr. Peter G. Danis, 634 N. Grand Blvd., St. Louis.
Place: St. Louis Medical Society Bldg. Time: First Friday of each month from October to June.

SEATTLE PEDIATRIC SOCIETY

President: Dr. Jay I. Durand, 1305–4th Ave., Seattle.
Secretary: Dr. Frederick B. Joy, 1215–4th Ave., Seattle.
Place: College Club. Time: Third Friday of each month, 6:30 p. m.

SOUTHWESTERN PEDIATRIC SOCIETY

President: Dr. Norman Nixon, 1136 W. 6th St., Los Angeles.
Secretary: Dr. Donald C. Shelby, 3780 Wilshire Blvd., Los Angeles.
Place: Jonathan Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

UNIVERSITY OF MICHIGAN PEDIATRIC AND INFECTIOUS DISEASE SOCIETY

President: Dr. Campbell Harvey, 35 W. Huron St., Pontiac, Mich.
Secretary: Dr. Harry A. Towsley, University of Michigan, Department of Pediatrics and Communicable Diseases, Ann Arbor, Mich.
Time: Autumn, 1941.

WESTCHESTER COUNTY MEDICAL SOCIETY, PEDIATRIC SECTION (NEW YORK)

President: Dr. John B. Ahouse, 27 Ludlow St., Yonkers, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye.
Place: Grasslands Hospital, Valhalla, N. Y. Time: Third Thursday in October, December, February and April.

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VOLUME 61 NUMBER 6

AMERICAN JOURNAL OF DISEASES OF CHILDREN

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JUNE 1941

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $8.00

Entered as Second Class Matter Jan. 4, 1911, at the Postoffice at Chicago, Under the Act of Congress of March 3, 1879

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